



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 40

Alan R. Katritzky

Advances in

Heterocyclic Chemistry

Volume 40

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Advances in

HETEROCYCLIC CHEMISTRY

Edited by

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1986



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Preface

Life begins at 40! Certainly for *Advances in Heterocyclic Chemistry* the fortieth volume marks some rather far-reaching changes in the series. These changes are described in detail in the introductory chapter "Advances in Heterocyclic Chemistry: Prospect and Retrospect" by your editor and Carol Drum, but it is appropriate to highlight the most important innovations in this preface. First, we have addressed the long-standing problem of indexing. Volume 40 contains a subject index for all the 40 regular volumes of the series together with the two supplementary volumes. Additionally, we have instituted an index of names of the contributors of chapters for our series, again spanning the whole 42 volumes. We have also completely revised the existing index of chapter titles. In the future, these three indexes will appear every five volumes; thus the next "index volume" will be 45. We believe that this procedure will provide the maximum benefit to readers of the series, while avoiding undue repetition.

Another major innovation is in the treatment of references. We have now adopted the novel style that was used for the first time in the monographs "Heterocyclic *N*-Oxides" (by your editor and J. M. Lagowski and published by Academic Press in 1971) and "Heteroaromatic Tautomerism," which was the first supplementary volume of this series. The method of treating references has been used more recently in "Comprehensive Heterocyclic Chemistry." It offers considerable advantages both for contributors and for readers: the reader can at a glance usually determine the year, the journal, and the page number, without looking the reference up. Naturally, complete details of all references are included at the end of each chapter.

The introductory chapter overviews the strategy and planning for the series, giving a chronological list of the titles that have appeared with notes on which have been updated and where updates are planned in the near future. Comments and suggestions from readers are welcomed by the editor. Finally, the introductory chapter makes suggestions for the preparation of reviews in the field of heterocyclic chemistry which are intended to provide some standard guidelines that might be adopted in appropriate cases throughout the literature of our subject.

Volume 40 also contains three more conventional chapters. Knabe reviews 1,2-dihydroisoquinolines in a chapter which updates the review by S. F. Dyke in Volume 14 of our series that appeared in 1972. Albert covers the chemistry of

4-amino-1,2,3-triazoles, which have not previously been the subject of an in-depth review. Finally, Speranza provides a most useful chapter on the gas-phase reactions of heteroaromatic compounds, a subject that has grown, in the last decade, from virtually nothing into a most important indication of the fundamental properties uncomplicated by solvent effects.

ALAN R. KATRITZKY

Advances in Heterocyclic Chemistry: Prospect and Retrospect

ALAN R. KATRITZKY AND CAROL A. DRUM

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I. Introduction

Since the first volume of *Advances in Heterocyclic Chemistry* appeared in 1963 much has happened to this subject. Enormous increases in our knowledge have occurred, not only in respect to factual information but also in our understanding of heterocyclic chemistry. We believe that our series of advances has helped to document and facilitate this increase in the quality and quantity of our knowledge.

The Series Editor, in consultation with the Editorial Board and with the publishers, has recently introduced into the series a number of rather important changes. It is one objective of this chapter to explain what effect these changes will have on the series.

Another major objective is to collect in one place guidelines which cover recommended arrangement of manuscripts of reviews of heterocyclic chemistry, including standard systematic treatment of scientific material under various headings.

Finally, we have been taking stock of our past coverage of different parts of the subject and we present a listing of chapters in preceding volumes together with an indication of how they have been updated and what further updating is proposed for the immediate future. It is hoped that this will be useful to readers wishing to gain access to the newest information on a variety of topics.

II. Innovations

A. HEADINGS

Readers will have noted that, as of Volume 37, the number of headings given in the contents pages at the start of each chapter has been increased. The purpose of this is to offer readers an easier way to access individual pieces of information. It is designed to be used much as an index would be (see next section).

B. INDEX VOLUMES

Starting with Volume 40, every fifth volume of the series will be designated an "Index Volume" and will contain, in addition to normal chapters, three indices as follows.

1. *Index of Chapter Titles*

This index at present appears in every volume of the series. It will be revised and in the future will appear only every five volumes. The index will continue to be cumulative covering every volume up to that particular volume.

2. *Index of Contributing Authors*

We plan to start a completely new index which will list authors who have written chapters in the series. This will also be cumulative, and will appear in every fifth volume.

3. *Subject Index*

The series has not for many years possessed a subject index. In a series of this type in which any one volume contains contributions on a number of disparate topics, a subject index covering a single volume is not especially useful. However, a subject index appearing periodically should be of considerably greater utility to readers. Therefore, with Volume 40, subject indexes will appear in every fifth volume. The subject index for Volume 40 will be cumulative, covering Volumes 1–40; subsequent subject indices will cover just the preceding five volumes, e.g., that of Volume 45 will cover Volumes 41–45.

C. REFERENCES

1. *Format*

For *Advances in Heterocyclic Chemistry*, starting with Volume 40, the reference citation system previously used in the monographs "Heteroaromatic *N*-Oxides" (by A. R. Katritzky and J. M. Lagowski, Academic Press, 1971) and "Tautomerism of Heterocycles" (by J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, Academic Press, 1976), and in "Comprehensive Heterocyclic Chemistry" (edited by A. R. Katritzky and C. W. Rees, Pergamon, 1984) will be used. In this system, each time a reference is cited in the text there appears in parentheses a two-letter code assigned to the journal being cited which is preceded by the year (tens and units only except for pretwentieth century references) and followed by the page number. For example: "It was shown (80TL1327) that" In this phrase, "80" refers to 1980, "TL" to Tetrahedron Letters and "1327" to the page number. For those journals which are

published in parts, or which have more than one volume number per year, the appropriate part or volume should be indicated, e.g., as in [73J(P2)1594] or [78JM(162)G11], where the first example refers to *J. Chem. Soc., Perkin Trans. 2*, page 1594 (1973), and the second to *J. Organometal. Chem.* Volume 162, page 611 (1978). Table references are designated by superscript letters which will be given as footnotes to each table, according to the same codes.

This reference system is being adopted because it is far more useful to the reader than the conventional "superscript number" system previously used in *Advances in Heterocyclic Chemistry*. It enables the reader to go directly to the literature reference cited, without first having to consult the bibliography at the end of each chapter. Another advantage is that it easily enables references to be added or subtracted at any time up to final submission of the manuscript, without altering the numbering system.

In each chapter bibliography, the references should be ordered numerically and alphabetically according to year, journal code, and page number in that sequence, preceded by the code used in the text; see examples at the end of this section.

Books, theses, etc. will be listed under the code MI (miscellaneous) starting each year and numbered 1, 2, 3 arbitrarily. Patents will be given three-letter codes as listed later; *Chemical Abstracts* references will be included for all patents using the usual code (CA).

Reference citations in the text should normally appear at the end of sentences. When authors' names are mentioned in the text, *et al.* should be used if there are more than two authors. When the name of the senior author is used rather than that of the first-named author of the paper, the word co-workers should be used in place of *et al.* However, all authors' names should be listed in the literature references, unless there are more than ten authors.

2. Journal Codes

The following journal codes will be used:

ABC	<i>Agric. Biol. Chem.</i>	ANY	<i>Ann. N. Y. Acad. Sci.</i>
ACH	<i>Acta Chim. Acad. Sci. Hung.</i>	AP	<i>Arch. Pharm. (Weinheim, Ger.)</i>
ACR	<i>Acc. Chem. Res.</i>	APO	<i>Adv. Phys. Org. Chem.</i>
AC(R)	<i>Ann. Chim. (Rome)</i>	AX	<i>Acta Crystallogr.,</i>
ACS	<i>Acta Chem. Scand.</i>	AX(B)	<i>Acta Crystallogr., Part B</i>
ACS(B)	<i>Acta Chem. Scand., Ser. B</i>	B	<i>Biochemistry</i>
AF	<i>Arzneim.-Forsch.</i>	BAP	<i>Bull. Acad. Pol. Sci., Ser.</i>
Ag	<i>Angew. Chem.</i>		<i>Sci. Chim.</i>
AG(E)	<i>Angew. Chem., Int. Ed. Engl.</i>	BAU	<i>Bull. Acad. Sci. USSR, Div.</i>
AHC	<i>Adv. Heterocycl. Chem.</i>		<i>Chem. Sci.</i>
AJC	<i>Aust. J. Chem.</i>	BBA	<i>Biochim. Biophys. Acta</i>
AK	<i>Ark. Kemi</i>	BBR	<i>Biochem. Biophys. Res. Commun.</i>

- | | | | |
|--------|---|---------|--|
| BCJ | <i>Bull. Chem. Soc. Jpn.</i> | JAP | <i>Jpn. Pat.</i> |
| BEP | <i>Belg. Pat.</i> | JAP(K) | <i>Jpn. Kokai</i> |
| BJ | <i>Biochem. J.</i> | JBC | <i>J. Biol. Chem.</i> |
| BJP | <i>Br. J. Pharmacol.</i> | JCP | <i>J. Chem. Phys.</i> |
| BRP | <i>Br. Pat.</i> | JCR(S) | <i>J. Chem. Res. (S)</i> |
| BSB | <i>Bull. Soc. Chim. Belg.</i> | JCS | <i>J. Chem. Soc.</i> |
| BSF | <i>Bull. Soc. Chim. Fr.</i> | JCS(C) | <i>J. Chem. Soc. (C)</i> |
| BSF(2) | <i>Bull. Soc. Chim. Fr.</i> | JCS(D) | <i>J. Chem. Soc., Dalton Trans.</i> |
| C | <i>Chimia</i> | JCS(F1) | <i>J. Chem. Soc., Faraday Trans. 1</i> |
| CA | <i>Chem. Abstr.</i> | JCS(P1) | <i>J. Chem. Soc., Perkin Trans. 1</i> |
| CB | <i>Chem. Ber.</i> | JGU | <i>J. Gen. Chem. USSR (Engl. Transl.)</i> |
| CC | <i>J. Chem. Soc., Chem. Commun.</i> | JHC | <i>J. Heterocycl. Chem.</i> |
| CCC | <i>Collect. Czech. Chem. Commun.</i> | JIC | <i>J. Indian Chem. Soc.</i> |
| CCR | <i>Coord. Chem. Rev.</i> | JMC | <i>J. Med. Chem.</i> |
| CHE | <i>Chem. Heterocycl. Compd. (Engl. Transl.)</i> | JMR | <i>J. Magn. Reson.</i> |
| CI(L) | <i>Chem. Ind. (London)</i> | JOC | <i>J. Org. Chem.</i> |
| CJC | <i>Can. J. Chem.</i> | JOM | <i>J. Organomet. Chem.</i> |
| CL | <i>Chem. Lett.</i> | JOU | <i>J. Org. Chem. USSR (Engl. Transl.)</i> |
| CPB | <i>Chem. Pharm. Bull.</i> | JPC | <i>J. Phys. Chem.</i> |
| CR | <i>C. R. Hebd. Seances Acad. Sci.</i> | JPR | <i>J. Prkat. Chem.</i> |
| CR(C) | <i>C. R. Hebd. Seances Acad. Sci., Ser. C.</i> | JPS | <i>J. Pharm. Sci.</i> |
| CRV | <i>Chem. Rev.</i> | JSP | <i>J. Mol. Spectrosc.</i> |
| CS | <i>Chem. Ser.</i> | JST | <i>J. Mol. Struct.</i> |
| CSC | <i>Cryst. Struct. Commun.</i> | K | <i>Kristallografiya</i> |
| CSR | <i>Chem. Soc. Rev.</i> | KGS | <i>Khim. Geterosikl. Soedin</i> |
| CZ | <i>Chem. Ztg.</i> | LA | <i>Liebigs Ann. Chem.</i> |
| DIS | <i>Disst. Abstr.</i> | M | <i>Monatsh. Chem.</i> |
| DIS(B) | <i>Diss. Abstr. Int. B</i> | MI | <i>Miscellaneous [book/journal]</i> |
| DOK | <i>Dokl. Akad. Nauk SSSR</i> | MIP | <i>Miscellaneous Pat.</i> |
| E | <i>Experientia</i> | MS | <i>Q. N. Porter and J. Baldas, 'Mass Spectrometry of Heterocyclic Compounds,' Wiley, NY 1971</i> |
| EGP | <i>Ger. (East) Pat.</i> | N | <i>Naturwissenschaften</i> |
| EUP | <i>Eur. Pat.</i> | NEP | <i>Neth. Pat.</i> |
| FES | <i>Farmaco Ed. Sci.</i> | NJC | <i>Nouv. J. Chim.</i> |
| FOR | <i>Fortschr. Chem. Org. Naturst.</i> | NKK | <i>Nippon Kagaku Kaishi</i> |
| FRP | <i>Fr. Pat.</i> | NMR | <i>T. J. Batterham, 'NMR Spectra of Simple Heterocyclic Compounds,' Wiley, NY 1971</i> |
| G | <i>Gazz. Chim. Ital.</i> | OMR | <i>Org. Magn. Reson.</i> |
| GEP | <i>Ger. Pat.</i> | OMS | <i>Org. Mass Spectrom.</i> |
| H | <i>Heterocycles</i> | OPP | <i>Org. Prep. Proced. Int.</i> |
| HC | <i>Chem. Heterocycl. Compd.</i> | OR | <i>Org. React.</i> |
| HCA | <i>Helv. Chim. Acta</i> | OS | <i>Org. Synth.</i> |
| HOU | <i>Methoden Org. Chem. (Houben-Weyl)</i> | OSC | <i>Org. Synth., Coll. Vol.</i> |
| IC | <i>Inorg. Chem.</i> | P | <i>Phytochemistry</i> |
| IJC | <i>Indian J. Chem.</i> | PAC | <i>Pure Appl. Chem.</i> |
| IJC(B) | <i>Indian J. Chem., Sect. B</i> | PC | <i>Personal Communication</i> |
| IJS | <i>Int. J. Sulfur Chem.</i> | PH | <i>'Photochemistry of Heterocyclic Compounds,' (O. Buchardt, ed.), Wiley, NY 1976</i> |
| IJS(B) | <i>Int. J. Sulfur Chem., Part B</i> | | |
| IZV | <i>Izv. Akad. Nauk SSSR Ser. Khim.</i> | | |
| JA | <i>J. Am. Chem. Soc.</i> | | |

PIA	<i>Proc. Indian Acad. Sci.</i>	SST	<i>Org. Compd. Sulphur, Selenium, Tellurium [R. Soc. Chem. series]</i>
PIA(A)	<i>Proc. Indian Acad. Sci., Sect. A</i>		
PMH	<i>Phys. Methods Heterocycl. Chem.</i>	T	<i>Tetrahedron</i>
PNA	<i>Proc. Natl. Acad. Sci. USA</i>	TH	<i>Thesis</i>
PS	<i>Phosphorus Sulfur</i>	TL	<i>Tetrahedron Lett.</i>
QR	<i>Q. Rev., (Engl. Transl.)</i>	UKZ	<i>Ukr. Khim. Zh. (Russ. Ed.)</i>
RCR	<i>Russ. Chem. Rev. (Engl. Transl.)</i>	UP	<i>Unpublished Results</i>
RRC	<i>Rev. Roum. Chim.</i>	USP	<i>U. S. Pat.</i>
RTC	<i>Recl. Trav. Chim. Pays-Bas</i>	YZ	<i>Yakugaku Zasshi</i>
S	<i>Synthesis</i>	ZC	<i>Z. Chem.</i>
SA	<i>Spectrochim. Acta</i>	ZN	<i>Z. Naturforsch.</i>
SA(A)	<i>Spectrochim. Acta Part A</i>	ZN(B)	<i>Z. Naturforsch., Teil B</i>
SAP	<i>S. Afr. Pat.</i>	ZOB	<i>Zh. Obshch. Khim. Lett.</i>
SC	<i>Synth. Commun.</i>	ZOR	<i>Zh. Org. Khim.</i>
SH	<i>W. L. F. Armarego, 'Stereochemistry of Heterocyclic Compounds,' Wiley, NY Parts 1 and 2</i>	ZPC	<i>Hoppe-Seyler's Z. Physiol. Chem.</i>

3. Journal Title Abbreviations

Abbreviations of titles of journals should generally follow the forms adopted by *Chemical Abstracts*.

Secondary references should be avoided if possible. If an original source is not examined, the secondary source should be given along with the original reference; if possible, a secondary source should in any case be given for references to originals in Russian, Japanese, and other less widely read languages.

Authors' initials should always precede the surname. Commas should be placed after the surname, except when a reference contains only two authors. The word "and" should precede the last name of all multiauthored references. There should be a comma after the volume number *or* after the abbreviated journal title *if* there is no volume number (not both). The year should always appear at the end of references to journals, in parentheses. (See examples below).

For Chemical Society publications, the following shortened forms should be used: *J. C. S. Perkin 1* (or *Perkin 2*, *Faraday 1* or *2*, *Dalton*), *J. C. S. Chem. Commun.*, i.e., abbreviate in the current Chemical Society style. References to *Chemical Abstracts* and other secondary sources should follow the original reference in square brackets []. *Chemical Abstracts* is abbreviated *CA* (no stops, underlined for italics). In deciding whether a *CA* reference should be given, authors should use their own judgement as to its usefulness to the reader. The decision depends on whether the original is widely accessible and whether further useful information could be obtained from the *abstract*. When citing abstract numbers in *CA* references, it is unnecessary to include the letter with the number (e.g., *CA 82 38947*, not *CA 82 38947b*).

III. Preparation and Arrangement of Manuscripts of Reviews of Heterocyclic Chemistry

A. SUBDIVISIONS OF MANUSCRIPT

Manuscripts should be divided into sections and, where desirable, into subsections, each having a short descriptive title. The scheme for the designation of subdivisions in *Advances in Heterocyclic Chemistry* is I,A,1,a etc., and this is convenient and precise. Cross references to other parts of a manuscript should refer to section numbers (e.g., Section II,A,2).

B. SCIENTIFIC ARRANGEMENT OF MATERIAL IN REVIEWS OF HETEROCYCLIC CHEMISTRY

Reviews often deal with a particular group of compounds based on a single ring or group of closely related ring systems. We believe that it is frequently advantageous to introduce a measure of uniformity in dealing with the various topics that arise in such a chapter. The method suggested below is adapted from that originally used in the text "Principles of Heterocyclic Chemistry" (by A. R. Katritzky and J. M. Lagowski, published by Methuen of which the American edition was published by Academic Press in 1968). A development of this system has been used in "Comprehensive Heterocyclic Chemistry."

1. Section on Structure

This will generally include the following main divisions:

- (i) Theoretical methods: critical appraisal of utility.
- (ii) Molecular dimensions: X-ray diffraction, neutron diffraction, microwave spectroscopy.
- (iii) Molecular spectra: NMR (^1H , ^{13}C , etc.), UV, IR, mass, photoelectron.
- (iv) Thermodynamic aspects (a): stability, ring strain, aromaticity.
- (v) Thermodynamic aspects (b): shape and conformation, especially of saturated and partially saturated compounds.
- (vi) Tautomerism: prototropic (annular and ring-substituent), ring-chain.
- (vii) Betaine and other unusual structures.

2. *Section on Reactivity*

This will be subdivided as follows:

a. *Reactivity at the Ring Atoms*

- (i) General survey.
- (ii) Thermal and photochemical reactions involving no other species.
- (iii) Toward electrophiles (including oxidants).
- (iv) Toward nucleophiles (including reducing agents).
- (v) Toward free radicals, electron-deficient species (carbenes, etc.) and at surfaces.
- (vi) Reactions with cyclic transition states.

b. *Reactivity of Substituents*

- (i) General survey of the effect of rings on reactions of substituents.
- (ii) Survey of the effect of rings on reactions of individual substituents in the following order: fused benzene rings; C-linked (alkyl, aryl, acyl, carboxy, cyano); N-linked (nitro, amino); O-linked (hydroxy, alkoxy); S-linked; halogen; metals; fused heterocyclic rings.

3. *Section on Synthesis*

- a. From acyclic and carbocyclic precursors
- b. From other heterocyclic compounds

4. *Section of Applications*

IV. **Figures, Tables, Equations, Chemical Formulae, and Abbreviations**

A. PREPARATION OF FIGURES AND TABLES

Detailed notes on their preparation are available from the Series Editor. All figures should be numbered in one sequence, and furnished with a descriptive legend.

Tables should be numbered, using roman numerals, in order of their mention in the text, and given a brief title. Extensive tables are not encouraged in *Advances in Heterocyclic Chemistry*, where the aim is to facilitate retrieval of information and to appraise the literature critically, rather than to duplicate it.

B. CHEMICAL STRUCTURES, EQUATIONS, AND SCHEMES

1. Drawings

The author's own drawings are now frequently photocopied for use in the final copy, and such drawings should be submitted in camera-ready format. The following guidelines are applicable to heterocyclic chemistry manuscripts designed for *Advances* and for elsewhere.

Blocks should be arranged in sequence as they are to appear in the text, with their location clearly indicated. Structures that are mentioned in the text should be numbered in sequence using arabic numbers, marked for bold-face type, enclosed in parentheses, and centered beneath the formulae. In the text, structures should be referred to by these numbers. Formulae that are not mentioned in the text need not be numbered.

Bonds in the structures must be angled correctly. Heteroatoms should be placed within, not outside, the framework of a ring. In writing formulae within a text line avoid vertical side chains. Use, for example, $\text{CH}_3\text{C}(=\text{CH}_2)\text{CH}_2\text{CH}=\text{CHCOOH}$.

Economy is needed in the use of structures both as regards their total number, and as regards their arrangement in blocks. A block with just one structure can occupy as much space as one with five structures, hence judicious combining of blocks can be very cost-effective. Do not unnecessarily repeat in an equation what has been written in the text. Reagents and reaction conditions can be either mentioned in the text, or written over an arrow in an equation, but not both.

Orient formulae so that the principal heteroatom is at the bottom and the numbering proceeds counterclockwise around the ring. Always write in double bonds, do not use circles in rings. For "mesoionic compounds," give (one of) the most important canonical forms. Do not use "semipolar bonds," i.e., use $\text{N}^+ - \text{O}^-$, and not $\text{N} \rightarrow \text{O}$ for *N*-oxides.

Draw formulae in the correct tautomeric form, i.e., the predominant structure for aqueous solution or the crystalline state (if in doubt, see "The Tautomerism of Heterocycles," by Elguero, Marzin, Katritzky, and Linda, Supplement 1, this series, 1976).

2. Numbering

Reaction equations (by which we mean a *balanced* [mass, charge] chemical reaction) should be numbered, if reference is made to them in the text, by Arabic numbers enclosed in parentheses, e.g., (1), written to the right of the

equation. They should be referred to in the text as Eq. (1) or Eqs. (3)–(5). Mathematical and chemical equations should be numbered in one sequence. Systems of interrelated chemical equations in sequence, with intermediates ($A \rightarrow B \rightarrow C \dots$), are referred to as schemes and should be numbered in a separate sequence, with, e.g., SCHEME 1, centered beneath the scheme and mentioned in the text as (Scheme 1). For reference in the text, individual formulae of an equation or scheme should be numbered in the same sequence as the isolated formulae.

3. *Placement in Text*

Pay careful attention to the layout of schemes and formulae, taking into account the width of the printed page. Both cramped structures and wasted space should be avoided. When reference is made subsequently to a structure already numbered, then just give the number, do not redraw the structure.

In the submitted manuscript, formula blocks, equations, etc. should be placed in the text between paragraphs, close to their mention. However, since precise placement of formulae in the printed text is not always possible, authors should use numbering to avoid having the formulae, equations, and schemes read as part of the text.

C. ABBREVIATIONS OF UNITS; SYMBOLS, CONVENTIONS

1. *Abbreviations of Units and Their Use with Figures*

When used in conjunction with numerals, abbreviations should be used for internationally accepted units. The following forms are suggested: %, cm, cm³, gm, mg, kg, ml, °C, cal, kcal. Periods are not used with these abbreviations. Write out liter and inches. Where units of measurement are referred to in the text in general terms with no specific numeral attached, they should be written out.

2. *Symbols*

For elements, use the internationally agreed (English) symbols, e.g., use I (not J) for iodine. A "generalized" metal is M (not Me). For isotopes, ¹³C (not C¹³) is correct. D may be used instead of ²H.

Much space can be saved by the proper use of abbreviated symbols for organic groups. The following are recommended: Me (methyl), Et (ethyl), Ph (phenyl), and Ar (generalized Aryl). For benzoyl use PhCO and for benzyl, PhCH₂ (Bz can be confused for both). Ac is acetyl, not "generalized acyl." When two different groups are designated by "R," use R and R' (prime); for three or more groups, use R¹, R², etc. (not R₁, R₂, R₃, wherein the last implies three Rs). When a group takes part in a reaction that is being illustrated, it is best to write it out fully, e.g., CH₃, rather than Me.

Often several structures can be combined into one by the use of generalizing symbols, such as R for substituents and Z for different heteroatoms in a ring. Indicate under the structure, if necessary, the identity of these general symbols. Do not use more than two such symbols in any formula.

3. Terminology

In general, the terminology should follow that used in the most recent Subject Index of *Chemical Abstracts*. If, for a valid reason you deviate from this, explain by a footnote at the beginning of your chapter.

V. Past Coverage and Future Program

This chapter concludes with a complete list of the articles which have appeared in this series through Volume 40. For each title, we have also given details of subsequent reviews in *Advances in Heterocyclic Chemistry*, corresponding sections in "Comprehensive Heterocyclic Chemistry" and reviews in other publications.

The following symbols explain why certain subjects which appeared in Volumes 1–25 have not been updated since 1979:

- L: The topic is now considered too long for coverage in an individual chapter in *Advances in Heterocyclic Chemistry*.
- S: This was a specialized topic and no update is planned.
- C: We consider that this topic has been adequately covered in other recent reviews and, therefore, no updating chapter is planned in *Advances in Heterocyclic Chemistry* in the immediate future.
- P: Chapter has been commissioned and is in preparation for a subsequent volume in *Advances in Heterocyclic Chemistry*.
- *: Under consideration of an update chapter at present time.

A LIST OF ARTICLES THAT HAVE APPEARED IN ADVANCES IN HETEROCYCLIC CHEMISTRY, VOLUMES 1-40

<i>Advances in Heterocyclic Chemistry</i>				Subsequent Reviews	
				<i>Adv. Heterocycl. Chem.</i>	<i>Compr. Heterocycl. Chem. (1984)</i>
Volume	Year	Pages	Subject	Volume Year Pages	Section and other references
1	1963	1-124	Thiophenes	L	3.13-3.15
1	1963	125-165	Acetylenecarboxylic Esters with Nitrogen Heterocycles	23, 1978, 263-482	
1	1963	167-188	Heterocyclic Pseudobases	25, 1979, 1-82	
1	1963	189-251	Aza Analogs of Pyrimidine and Purine Bases of Nucleic Acids	S	2.13
1	1963	253-309	Quinazolines	24, 1979, 1-62	
1	1963	311-340	Prototropic Tautomerism—General	Suppl. 1, 1976, 1-70	
1	1963	341-437	Prototropic Tautomerism—Six-Membered Rings	Suppl. 1, 1976, 71-213	5.08
2	1963	1-26	Prototropic Tautomerism-Five-Membered Rings with One Hetero Atom	Suppl. 1, 1976, 214-265	
2	1963	27-81	Prototropic Tautomerism-Five-Membered Rings with Two or More Hetero Atoms	Suppl. 1, 1976, 266-501	
2	1963	83-130	Three-Membered Rings with Two Hetero Atoms	24, 1979, 63-107	2.14, 79M11
2	1963	131-177	Free-Radical Substitutions of Heteroaromatics	16, 1974, 123-180	
2	1963	179-202	Action of Metal Catalysts on Pyridines	S	
2	1963	203-244	Quinoxalines	22, 1978, 376-431	2.14, 79M11
2	1963	245-286	Reactions of Diazomethane with Heterocyclic Compounds	*	

2	1963	287-309	Acid-Catalyzed Polymerization of Pyrroles and Indoles	S	3.05
2	1963	311-342	1,3-Oxazines	23, 1978, 1-53	2.27
2	1963	343-364	Selenazoles	24, 1979, 109-150	4.20
2	1963	365-422	Isoxazoles	25, 1979, 147-204	4.16
3	1964	1-56	Quaternization of Heterocycles	22, 1978, 71-121	
3	1964	57-78	Reactions of Heterocyclic Compounds with Carbenes	*	82KGS723
3	1964	79-207	Carbolines	*	3.09
3	1964	209-261	Applications of Hammett Equation to Heterocycles	20, 1976, 1-64	
3	1964	263-284	1,2,3,4-Thiatriazoles	20, 1976, 145-174	4.24-4.28
3	1964	285-371	Nucleophilic Heteroaromatic Substitution	34, 198, 305-444	
3	1964	373-383	Pentazoles	S	4.14
4	1965	1-42	Covalent Hydration in Nitrogen Heteroaromatics	20, 1976, 117-143	
4	1965	43-73	Covalent Hydration in Nitrogen Heteroaromatics	20, 1976, 117-143	
4	1965	75-106	Oxazolones	21, 1977, 175-206	4.18
4	1965	107-120	Isothiazoles	14, 1972, 1-41	4.17
4	1965	121-144	Hetarynes	C	71AG(E)20 82T427 76UKZ122
4	1965	145-423	Reactivity of Azine, Benzoazine and Azinoazine Derivatives with Simple Nucleophiles	34, 1984, 305-444	
5	1965	1-67	Electronic Structure of Heterocyclic Sulfur Compounds	P	
5	1965	69-118	Theoretical Studies of Physicochemical Properties and Reactivity of Azines	P	
5	1965	119-204	1,2,4-Thiadiazoles	32, 1982, 285-398	4.25
5	1965	205-290	Aminochromes	*	

(continued)

A LIST OF ARTICLES (continued)

Advances in Heterocyclic Chemistry				Subsequent Reviews	
				Adv. Heterocycl. Chem.	Compr. Heterocycl. Chem. (1984)
Volume	Year	Pages	Subject	Volume Year Pages	Section and other references
5	1965	291-314	Aromatic Quinolizines	31, 1982, 1-62	2.10
5	1965	315-367	Pyrrolizidines	24, 1979, 248-291	3.18
6	1966	1-43	Physicochemical Aspects of the Chemistry of Purines	24, 1979, 215-246	
6	1966	45-93	Reduction of Nitrogen Heterocycles with Complex Metal Hydrides	39, 1986, 1-77	
6	1966	95-146	Heterocyclic Syntheses with Nitrilium Salts and Nitriles	S	
6	1966	147-227	Cyclic Enamines and Imines	S	
6	1966	229-345	Substitution in the Pyridine Series	C	
6	1966	347-429	Pyrazoles	C	4.04-4.05
7	1966	1-37	Halogenation of Heterocyclic Compounds	*	
7	1966	39-151	1,2- and 1,3-Dithiolium Ions	27, 1980, 151-239	4.31-4.32
7	1966	153-181	Diquinolylmethane and Its Analogs	S	
7	1966	183-224	1,3,4-Oxadiazoles	P	4.23
7	1966	225-299	Literature of Heterocyclic Chemistry	25, 1979, 303-391	1.03
7	1966	301-376	Mass Spectrometry of Heterocycles	L	74H473 78KGS1443
					71MI1 71MI2
7	1966	377-490	Chemistry of Furans 1952-1963	30, 1982, 167-238 31, 1982, 237-344	3.10-3.12
8	1967	1-19	Heterocyclic Diazo Compounds	*	82H559
8	1967	21-82	Diazepines	P	5.16 84MI2

8	1967	83-113	Phenoxazines	•	2.27
8	1967	115-142	Hilbert-Johnson Reaction of 2,4-Dialkoxypyrimidines with Hologenoses	S	
8	1967	143-163	Claisen Rearrangements in Nitrogen Heterocycles	S	77S589
8	1967	165-217	Cyclic Peroxides	*	
8	1967	219-276	Monocyclic Sulfur-Containing Pyrones	34, 1984, 145-303	2.25-4.16, 4.02
8	1967	277-379	Indoxazenes and Anthranils	29, 1981, 1-69	
9	1968	1-25	Reissert Compounds	24, 1979, 187-214	
9	1968	27-105	Monoazaindoles: Pyrrolopyridines	•	3.08, 3.09
9	1968	107-163	1,2,5-Thiadiazoles	C	4.26
					83H71
9	1968	165-209	1,3,4-Thiadiazoles	C	4.27
9	1968	211-320	Pyridazines	24, 1979, 363-456	2.12
9	1968	321-460	Phenothiazines	P	2.27
10	1969	1-41	Benzofuroxans	29, 1981, 251-340	4.22
10	1969	43-112	Indole Grignard Reagents	S	
10	1969	113-147	Isoindoles	29, 1981, 341-399	3.04-3.06
					81UK2073
10	1969	149-198	Pyridopyrimidines: 1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-Triazanaphthalenes	C	2.13
10	1969	199-240	Cyclic Hydroxamic Acids	*	74AG(E)376
10	1969	241-326	Pyrylium Salts	Suppl. 2, 1982	2.22-2.24
11	1970	1-121	Photochemistry of Heterocycles	30, 1982, 239-317	76M11
				33, 1983, 1-93	73PAC339
11	1970	123-175	Naphthyridines	33, 1983, 95-184	2.11
11	1970	177-381	Benzo[b]thiophenes	29, 1981, 171-249	3.13-3.15
11	1970	383-472	Physicochemical Properties of Pyrroles	L	3.01
11	1970	473-523	Quinuclidines		2.04
12	1970	1-41	Selenophenes	30, 1982, 127-166	3.16
12	1970	43-101	3-Piperideines (1,2,3,6-Tetra- hydropyridines)	S	

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A LIST OF ARTICLES (continued)

Advances in Heterocyclic Chemistry				Subsequent Reviews	
				Adv. Heterocycl. Chem.	Compr. Heterocycl. Chem. (1984)
Volume	Year	Pages	Subject	Volume Year Pages	Section and other references
12	1970	103-183	Imidazoles	27, 1980, 241-326	4.06-4.08
12	1970	185-212	Lactim Ethers	S	
12	1970	213-316	Electrolysis of <i>N</i> -Heterocycles	36, 1984, 235-341	730E563
13	1971	1-44	Heterocyclic Ferrocenes	S	
13	1971	45-76	1-Azirines	C	5.04 83CHE215
13	1971	77-159	Electronic Aspects of Purine Tautomerism	18, 1975, 199-335 Suppl. 1, 1976, 502-550	
13	1971	161-234	1,6,6aS ^{IV} -Trithiapentalenes	C	4.38
13	1971	235-314	Electrophilic Substitutions of Five-Membered Rings	*	3.02
13	1971	315-413	Phenanthridines	*	2.04-2.08
14	1972	1-41	Mononuclear Isothiazoles	C	4.17
14	1972	43-98	Benzisothiazoles	38, 1985, 135-176	4.17
14	1972	99-209	Pyrazines	C	2.14 82MI1
14	1972	211-278	Heterocycles by Ring Closure of ortho-Substituted <i>t</i> -Anilines	S	
14	1972	279-329	1,2-Dihydroisoquinolines	S	
14	1972	331-381	Benzo[<i>c</i>]thiophenes	C	3.13-3.15
15	1973	1-65	Heterocyclic Oligomers	S	
15	1973	67-98	Oxidation of Monocyclic Pyrroles	S	3.05-3.06
15	1973	99-136	4-Oxy- and 4-Keto-1,2,3,4- tetrahydroisoquinolines	S	

15	1973	137-185	One-Step Isotopic Hydrogen Labeling of Heterocycles	*	
15	1973	187-231	1-Pyridines	*	
15	1973	233-276	Saccharin and Derivatives	S	
15	1973	277-324	NMR Spectroscopy of Indole and Its Derivatives	S	
16	1974	1-31	Base-Catalyzed Hydrogen Exchange		
16	1974	33-85	1,2,3-Triazoles	C	2.18 80MI1
16	1974	87-121	Nitrogen-Bridged Six-Membered Ring Systems: 7-Azabicyclo[2;2;1]-hepta-2,5-dienes, Naphthalen-1,4-imines and Anthracen-9,10-imines	C	
16	1974	123-180	Homolytic Substitution of Heteroaromatics	*	
16	1974	181-288	Dibenzothiophenes	C	3.13-3.15
16	1974	289-324	Cationic Polar Cycloaddition	*	
17	1974	1-26	2,3-Dihydro-1,4-Diazepines	C	5.16 84MI2
17	1974	27-43	1,5-Benzodiazepines	C	5.16 84MI2
17	1974	45-98	1-, 2-, and 3-Benzazepines	C	5.16 84MI1
17	1974	99-221	Oxazoles	C	4.18
17	1974	213-253	Heteroaromatic <i>N</i> -Imines	29, 1981, 71-139	
17	1974	255-356	Aromaticity of Heterocycles	*	
18	1975	1-58	Isatin	S	
18	1975	59-97	Thiochromanones and Related Compounds	S	2.25
18	1975	99-158	Thioureas in the Synthesis of Heterocycles	S	

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<i>Advances in Heterocyclic Chemistry</i>				Subsequent Reviews	
				<i>Adv. Heterocycl. Chem.</i>	<i>Compr. Heterocycl. Chem. (1984)</i>
Volume	Year	Pages	Subject	Volume Year Pages	Section and other references
18	1975	159-198	Chrom-3-enes	C	2.22-2.24 77MI1
18	1975	199-335	Tautomerism and Electronic Structure of Biological Pyrimidines	S	2.13
18	1975	337-482	Benzo[b]furan and Its derivatives	C	3.10-3.12
19	1976	1-122	Meso-Ionic Compounds	C	1.02 85T2239 82T2965 83KGS3
19	1976	123-214	Thienothiophenes	C	4.36
19	1976	215-278	1,2,3-Triazines	C	2.18
19	1976	279-371	Synthesis of Heterocycles with Acetylenic Esters	*	
20	1976	1-64	Applications of Hammett Equation to Heterocycles	*	
20	1976	65-116	1,2,4-Oxadiazoles	C	4.18
20	1976	117-143	Covalent Hydration in Nitrogen Heterocycles	*	
20	1976	145-174	1,2,3,4-Thiatriazoles	C	4.28
20	1976	175-319	Nomenclature of Heterocycles	C	1.02
21	1977	1-63	Pyrrolodiazines with a Bridgehead Nitrogen	S	4.05
21	1977	65-118	Thienopyridines	C	3.17
21	1977	119-173	Tellurophene and Related Compounds	C	3.16
21	1977	175-206	Oxazolones	C	4.18

21	1977	207-251	Isoxazolidines	C	4.16
21	1977	253-321	(2 + 2)-Cycloaddition and (2 + 2)- Cycloreversion Reactions of Heterocycles	*	
21	1977	323-435	Tetrazoles	C	4.13
21	1977	437-481	1,2-Dioxetanes	C	5.15
22	1978	1-69	Phenanthrolines	•	1.06; 1.11; 2.01 2.04; 2.05
22	1978	71-121	Quaternization of Heteroaromatics: Quantitative Aspects	•	
22	1978	123-181	Isatogens and Indolones	S	2.03-3.03; 3.03; 3.09
22	1978	183-320	Aromatic Azapentalenes	C	4.36
22	1978	321-365	Cyclazines and Related <i>N</i> -Bridged Annulenes	C	3.08
22	1978	367-431	Quinoxalines: 1963-1975	C	2.14 79MI2
23	1978	1-53	1,3-Oxazines	C	2.27
23	1978	55-102	π -Excessive Heteroannulenes	C	5.20
23	1978	103-170	Indolizines	C	3.08
23	1978	171-261	Olefin Synthesis with Anils	S	
23	1978	263-482	Reactions of Acetylene Carboxylic Esters with Nitrogen Heterocycles	•	
24	1979	1-62	Quinazolines	C	2.13
24	1979	63-107	Three-Membered Rings with Two Heteroatoms	C	5.08
24	1979	109-150	Selenium-Nitrogen Heterocycles	C	4.20
24	1979	151-185	Benzo[<i>c</i>]cinnolines	C	2.12
24	1979	187-214	Reisert Compounds: 1968-1978	C	81BSB609
24	1979	215-246	Physicochemical Aspects of Purines	S	4.09
24	1979	247-291	Pyrrolizidines	C	3.08; 3.05; 3.03
24	1979	293-361	1,4-Thiazines and Their Dihydro Derivatives	C	2.27

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A LIST OF ARTICLES (continued)

<i>Advances in Heterocyclic Chemistry</i>				Subsequent Reviews	
				<i>Adv. Heterocycl. Chem.</i>	<i>Compr. Heterocycl. Chem. (1984)</i>
Volume	Year	Pages	Subject	Volume Year Pages	Section and other references
24	1979	363-456	Pyridazines	C	2.12
25	1979	1-82	Heterocyclic Pseudobases	*	
25	1979	83-112	4-Thiazolidinones	C	4.19
25	1979	113-145	Ring Synthesis of Heteroaromatic Nitro Compounds	S	
25	1979	147-204	Isoxazoles: Since 1963	C	4.16
25	1979	205-301	Heteroaromatic Radicals: General Properties Radicals with Group V Ring Heteroatoms	27, 1980, 31-149	
25	1979	303-391	Literature of Heterocyclic Chemistry Part II	C	1.03
26	1980	1-113	Heterocyclic Betaine Derivatives of Alternant Hydrocarbons		4.37 85T2239
26	1980	115-133	Thiocoumarins		2.25
26	1980	135-241	Benzo[c]Furans		3.10-3.12
27	1980	1-29	1-Azabicyclo[3.1.0]hexanes and Analogs		
27	1980	31-149	Heteroaromatic Radicals: Radicals with Group VI and Groups V and VI Ring Heteroatoms		
27	1980	151-239	1,2- and 1,3-Dithiolium Ions		4.30-4.31
27	1980	241-326	Imidazoles		4.60-4.80
28	1981	1-71	Polyfluoroheteroaromatics		
28	1981	73-126	1,2- and 2,1-Benzothiazines		2.27
28	1981	127-182	Isatoic Anhydrides and Their Uses in Heterocyclic Synthesis		

28	1981	183-229	Reactions of Benzyne with Heterocycles	S	
28	1981	231-361	Carbenes and Nitrenes in Heterocyclic Chemistry: Intramolecular Reactions		
29	1981	1-69	Indoxazenes and Anthranils: 1966-1979		4.16
29	1981	71-139	Heteroaromatic <i>N</i> -Imines and <i>N</i> -Aminoazonium Salts		
29	1981	141-169	Mononuclear Heterocyclic Rearrangements		
29	1981	171-249	Benzo[<i>b</i>]thiophenes		3.13-3.15
29	1981	251-340	Furoxans and Benzofuroxans		4.22
29	1981	341-399	Isoindoles		3.04-3.06
30	1982	1-45	Azodicarbonyl Compounds in Heterocyclic Synthesis		
30	1982	47-78	Sulfur Transfer Reagents in Heterocyclic Synthesis		
30	1982	79-126	Heteroadamantanes		
30	1982	127-166	Selenophenes		3.16
30	1982	167-238	Furans, Part 1	31, 1982, 237-344	3.10-3.12
30	1982	239-317	Photochemistry of Nitrogen Heterocycles		
30	1982	319-402	Transition Organometallic Compounds in Heterocyclic Synthesis		
31	1982	1-62	Aromatic Quinolizines		2.10
31	1982	63-113	1,2-Dithiole-3-thiones and 1,2-Dithiol-3-ones		4.31
31	1982	115-167	Azocines		5.19
31	1982	169-206	Dewar Heterocycles and Related Compounds		
31	1982	207-236	Cyclizations Under Vilsmeier Conditions		
31	1982	237-344	Furans, Part 2		3.10-3.12
32	1982	1-81	Annulation of a Pyrimidine Ring to an Existing Ring		
32	1982	83-125	<i>gem</i> -Dithienylalkanes		

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A LIST OF ARTICLES (continued)

<i>Advances in Heterocyclic Chemistry</i>				Subsequent Reviews	
				<i>Adv. Heterocycl. Chem.</i>	<i>Compr. Heterocycl. Chem. (1984)</i>
Volume	Year	Pages	Subject	Volume Year Pages	Section and other references
32	1982	127-232	Syntheses of Tetracyclic and Pentacyclic Condensed Thiophenes		
32	1982	233-284	2 <i>H</i> - and 3 <i>H</i> -Pyrroles		
32	1982	285-398	1,2,4-Thiadiazoles		4.25
33	1983	1-93	Photochemistry of Oxygen- and Sulfur-Heterocycles		
33	1983	95-146	Reactivity of Naphthyridines toward Nitrogen Nucleophiles		2.11
33	1983	147-184	Naphthyridines		2.11
33	1983	185-239	Pseudoazulenes		
33	1983	241-330	Pyrido[1,2- <i>a</i>]pyrimidines		
34	1983	1-52	3 <i>H</i> -Pyrazoles		
34	1983	53-78	4 <i>H</i> -Pyrazoles		
34	1983	79-143	Triazolopyridines		4.15
34	1983	145-303	Pyrans, Thiopyrans and Selenopyrans		2.22-2.25
34	1983	305-444	Formation of Anionic σ -Adducts		
35	1984	1-81	Dibenzofurans		
35	1984	83-198	9 <i>H</i> -Carboazoles		3.10-3.12
35	1984	199-279	Four-Membered Rings Containing One Sulfur		5.14
35	1984	281-374	Bipyridines		
35	1984	375-412	2 <i>H</i> -Imidazoles		
35	1984	413-450	4 <i>H</i> -Imidazoles		
36	1984	1-173	Conformational Equilibria in N-Containing Saturated Six-Membered Rings		

36	1984	175-234	Phase Transfer Catalysis in Heterocycles	
36	1984	235-341	Electrolysis of <i>N</i> -Heterocycles, Part II	
36	1984	342-409	Pyrazolopyridines	4.05
37	1984	1-66	Pyrrolizines	3.03; 3.05; 3.08
37	1984	67-165	Arene Oxides	
37	1984	167-215	Synthesis of Pyridines by Electro- Chemical Methods	
37	1984	217-349	DELTA ² -1,2,3-Triazolines	4.11
37	1984	351-361	DELTA ³ - and DELTA ⁴ -1,2,3-Triazolines	4.11; 5.04
38	1985	1-103	Dihydroazines	
38	1985	105-133	Benzisothiazoles and Other Polycyclic Isothiazoles	4.17
38	1985	135-176	1,4-Benzothiazines, Dihydro-1,4- Benzothiazines, and Related Compounds	2.27
38	1985	177-228	Hydantoins	4.07; 4.06; 1.11
38	1985	229-297	Barbituric Acids	
38	1985	299-368	Heterocyclic β -Enamino Esters, in Heterocyclic Synthesis	
39	1986	181-236	Aziridines in the Synthesis of Natural Products	
39	1986	1-77	Reduction of Nitrogen Heterocycles with Complex Metal Hydrides	
39	1986	117-180	8-Azapurines	
40	1986	1-24	Advances in Heterocyclic Chemistry: Prospect and Retrospect	
40	1986	25-104	Reactivity of Heteroaromatic Compounds in the Gas Phase	
40	1986	105-128	1,2-Dihydroisoquinolines	
40	1986	129-197	4-Amino-1,2,3-Triazoles	

References

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The Reactivity of Heteroaromatic Compounds in the Gas Phase

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I. Introduction

A fundamental understanding of structure-reactivity and structure-energy correlations in heteroaromatic compounds is of central importance in chemistry and biochemistry. The classical approach to this subject normally

involves dissolving the heteroaromatic compound in a liquid medium, where a given reactant is added or generated. A reaction takes place whose rate or equilibria parameters are measured by means of the conventional techniques of physical organic chemistry. Although these techniques have yielded an enormous amount of valuable data, several problems limit their range of applicability and complicate their interpretation. In the first place, the range of structural effects that can be investigated in a given solvent is limited by interfering reactions between a heteroaromatic molecule and the reaction environment. Thus, for instance, direct electrophilic substitution at one carbon of a neutral azine base is virtually unknown. The position of possible tautomeric equilibria in heteroaromatic compounds is strongly determined by the proton-donor-acceptor properties of the solvent. Acidic media and the presence of catalysts normally yield undesired side products in electrophilic heteroaromatic substitutions and, in many cases, kinetically intractable reaction patterns. Furthermore, the course of many nucleophilic heteroaromatic substitutions conducted under strongly alkaline conditions may well be affected by the establishment of coexisting prototropic equilibria involving the conjugate base and the tautomeric forms of the heteroaromatic substrate. Consequently, much more is known about structural effects of those heteroaromatic compounds for which a sufficient insensitivity to environmental factors is combined with an adequate reactivity. Different solvent systems often determine orientation in heteroaromatic substitution, but the interpretation of this effect is hampered by several coexisting physical phenomena. For example, significant modification of simple physical properties of the organic substrate (e.g., the dipole moment), related to its electron density distribution, is observed, as well as formation of hydrogen bonding between substrate molecules, homoconjugate ion pairs, and counterion pairs.

A radical solution to all of the above-mentioned difficulties is to eliminate the solvent medium entirely and to measure structural effects on heteroaromatic reactivity in the gas phase. During the last decade, a revolution has occurred in the experimental and theoretical approaches to understanding gas-phase ion chemistry. This has occurred as the result of the simultaneous development of several experimental methods for studying organic ion-molecule kinetics and equilibria in the gas phase with precision and range of effects equivalent to or even better than that normally obtained in solution and by very sophisticated molecular orbital calculations. The importance of reactivity studies in the gas phase is twofold. Direct comparison of rates and equilibria in gaseous and condensed media reveals previously inaccessible effects of ion solvation. In addition, reactivity data in the gas phase provide a direct evaluation of the fundamental, intrinsic properties of molecules and represent a unique yardstick against which the validity of theoretical estimates of such properties can be adequately assayed.

In this article, attention is focused on structural effects in ionic heteroaromatic substitutions in the gas phase. A brief outline of several theoretical approaches to heteroaromatic reactivity is given in the next section, together with a critical evaluation of their predictive value. We shall also describe the most common experimental methods used in kinetic and equilibria measurements of gas-phase ionic processes. A brief presentation of the molecular properties of heteroaromatic compounds, and of their reactivity, is given in Section III. Special attention is focused in Section IV to gas-phase proton-transfer equilibria involving heteroaromatic compounds and their correlation with related solution data. The limited information presently available about gas-phase reactivity and orienting properties of simple heteroaromatics toward ionic reactants is presented in Section V, together with its relevance to theoretical predictions. A prognosis rather than a conclusion is included in the last section since—as will be immediately evident to the reader—the field of heteroaromatic reactivity in the gas phase is at such an early stage that this article can only serve as a point of departure.

II. Methodologies of Investigation

A. THEORETICAL CALCULATIONS

Theoretical calculations share with gas-phase kinetic and thermodynamic measurements the common aim of the understanding of the intrinsic reactivity properties of heteroaromatic compounds. The purpose of this subsection is to consider the predictive value of theoretical methods insofar as ionic substitution reactions on simple heteroaromatics are concerned. The topic under discussion is inherently limited by the wide range of interest in the understanding of the principles of these processes in solution. It is exactly in this field that an appropriate amount of data concerning gas-phase structural and reactivity properties of heteroaromatic compounds is at present available from modern experimental techniques that can be tested against theoretical predictions.

A wide range of molecular orbital calculations, of varying degree of complexity, have been used to estimate the molecular geometry and related physical properties of heteroaromatic molecules, as well as their electronic configuration and reactivity parameters. A number of general accounts of these theoretical achievements are available (61MI1; 68MI1; 69MI1; 70ACR217; 70MI1; 71PMH55; 74MI1; 75CB97; 75PAC767; 77MI1; 78CB396; 78MI1; 79MI1).

Two distinct approaches are generally employed in the theoretical analysis of heteroaromatic reactivity: the method of reactivity indices and potential surfaces.

1. *Reactivity Indices*

The reactivity indices method is based on the assumption of a direct correlation between the activation free energy of a process and some intrinsic parameters, called reactivity indices, related to the electronic properties of the heteroaromatic species involved in the process itself. Some indices, such as charge density, frontier electron density, polarizability, or free valence, pertain to electronic properties of the unperturbed neutral substrate, which is considered in an isolated state. Other indices, such as the localization energy, are related to the stability of the transitional or intermediate state of the substitution process, e.g., the π or σ complex in electrophilic substitution reactions (Fig. 1).

The total charge and the π -electron densities refer to the electron density at a given carbon obtained by summing up the contributions of the corresponding filled molecular orbitals (52QR63).

Electrophilic attack is considered to occur primarily at the site where the electron density is highest; the contrary is true for nucleophilic substitutions. Homolytic displacements are not considered to be appreciably affected by the electron-density distribution.

If only the electron density of the highest occupied molecular orbital (HOMO) is taken into account, an electrophilic attack is said to be regulated by the frontier electron density index (54JCP1433; 79FCF1). In nucleophilic substitutions, the aromatic substrate tends to accept an electron pair in the transition state, and so the frontier orbital is taken as the lowest unoccupied molecular orbital (LUMO). In this case, the frontier electron density is assumed to be as the electron distribution that would be present in the LUMO if it were occupied by two electrons. In contrast to arguments based on the charge or π -electron densities, both nucleophilic and electrophilic substitution occur preferentially at the atom with the highest electron density within the appropriate frontier orbital, i.e., LUMO or HOMO, respectively.

The localization energies refer to the energy difference between the isolated substrate molecule and the transition state complex. Reasonable estimates of the localization energies are obtained in the case where an experimental parameter for an appropriate description of the structure of the reaction intermediate (e.g., the σ complex) is available and when the intermediate structure is a suitable model of the transition state. In this event, the localization energy satisfactorily reflects the relative stability of the relevant

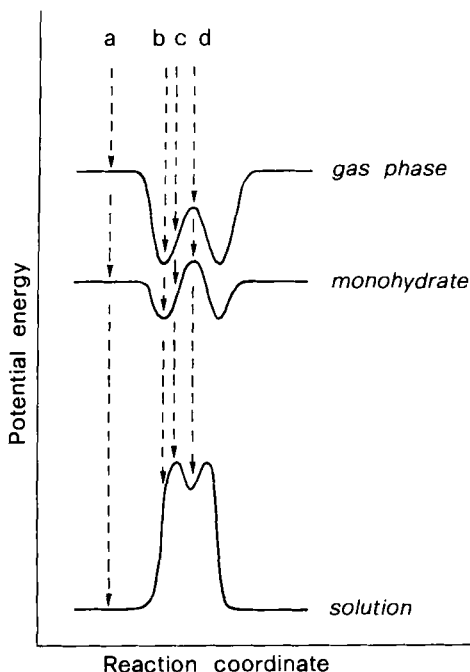


FIG. 1. Possible cases of energy profiles for the same reaction occurring in the gas phase and in solution. The arrows indicate the domain of validity of reactivity indices in (a) the isolated molecule approximation (charge and electron densities); (c) the transition state approximation; (d) the localization energy approximation. Arrow (b) indicates the range of application of the molecular electrostatic potential approach.

activated complex and, therefore, provides a reliable guide to predicting the orientation in the substitution reactions.

The reactivity indices discussed above imply different models of the transition state. The assumption that the charge density, or π -electron distribution, is the main factor controlling the reactant orientation implies that the transition state closely resembles the unperturbed molecule and that electrostatic interactions are an important orientational factor. The corresponding physical picture for correlations with frontier electron densities is less straightforward, since it involves an electron-transfer interaction between the reaction and a slightly perturbed aromatic system in which most of the bond conjugation is retained (54JCP1433; 59JCS2224,2232; 60JCP1743; 68JA223; 70FCF1; 77MI2). The intimate relationship between reactant orientation and localization energies implies that the transition state is very different from the initial state, since it reflects the structure of the σ

intermediate where the loss of bond conjugation is partly compensated by the formation of the new σ bond.

Reactivity indices are linked to the activation energy of the process, defined as the potential energy difference between the initial state and the transition complex, both considered in an isolated state. In other words, no allowance is made for the magnitude of the "entropy term" and for the contribution from solvation and ion pairing, which may significantly alter the energy profile of the substitution reaction (Fig. 1). A feasible situation can occur when the structure of the transition state is not satisfactorily identifiable with the structure of the σ intermediate or with that of the isolated substrate. When both approximations fail, application of reactivity indices may lead to a poor appraisal of the relative reactivity of organic compounds.

Finally, it should be considered that the reactivity indices have a theoretical justification, provided they treat alternate hydrocarbon systems (52MI1; 53MI1) where a uniform charge distribution and a "symmetric" location of filled and empty orbital levels can be envisaged (52MI1; 53MI1). The "asymmetric" distribution of charge and of molecular orbital levels, typical of heteroaromatic molecules, results in disappearance of any correspondence among the different indices and makes it necessary, in every instance, to conduct a separate analysis of the applicability of the methods employed in order to choose the most appropriate one for the theoretical description of reactivity.

2. *Potential Surfaces*

The method of potential surfaces is based on the evaluation of the interactions established within the encounter pair of a substitution process. A complete energy profile versus the reaction coordinate can be obtained only for gas-phase reactions involving simple species. A rigorous application to complex reactions, such as those involving heteroaromatic molecules, meets with some difficulties because of the time limitation allowed to computational analysis. Consequently, a number of simplifying approximations is necessary. However, with the ever increasingly powerful computers available, direct investigation of reaction profiles of heteroaromatic substitution reaction appears to be within reach. Several recent studies deal with the determination of the energy of an ion-molecule encounter pair as a function of the relative location of the ion, generally pictured as a point charge, with respect to the aromatic system of the neutral molecule (71T101; 71AG449; 72ZC67; 72ZC481; 74ZC481; 74MI2; 73IJQ923; 76JA388; 77MI4). If the analysis is restricted to the electrostatic potential established within the encounter pair, a map of equipotential curves can be constructed. From this we can predict the most favored sites and pathways of attack of ionic species on the aromatic

molecule (73MI1; 75CPL441). The molecular electrostatic potential is defined in Eq. (1),

$$V(\bar{r}) = \sum_A \frac{Z_A}{|R_A - \bar{r}|} - \int \frac{\rho(\bar{r}')}{|\bar{r}' - \bar{r}|} d\bar{r}' \quad (1)$$

where Z_A is the nuclear charge of atom A, located at R_A , and $\rho(\bar{r}')$ is the electronic density at the point r' . In terms of molecular orbitals Ψ_i , $V(\bar{r})$ represents the electrostatic potential

$$\rho(\bar{r}') = \sum_i N_i \Psi_i^*(\bar{r}') \Psi_i(\bar{r}') \quad (2)$$

that is produced at any point \bar{r} by the nuclei and electrons of the molecule in question. It is numerically equal to the energy of interaction of a positive point charge, of magnitude -1.0 electron units, with the unperturbed charge distribution of the molecule. When $V(\bar{r}) < 0$, it indicates an attractive interaction, while $V(\bar{r}) > 0$ indicates a repulsive one. Obviously, such a point charge would have some perturbing effect on the electronic density distribution in the molecule, so that $V(\bar{r})$ is actually the first-order interaction energy in a perturbation treatment of the system (73CPL419). Even though Eq. (1) is an exact expression for $V(\bar{r})$, the accuracy of the calculated potentials depends upon the quality of the approximate wave function that is used to compute $\rho(\bar{r})$.

B. PHOTOELECTRON SPECTROSCOPY

If a photon of frequency ν collides with a single molecule, electrons whose energies depend on the orbitals they occupy, as well as on ν , may be ejected. These electrons are known as photoelectrons, and the measurement of their energy spectra is known as photoelectron spectroscopy (74PMH1; 78MI2). Analysis of such spectra enables us to determine ionization potentials. Thanks to Koopmans' theorem they are equated to the energies of filled orbitals of the gaseous molecule (34MI1). Consequently, this appears to be a direct method for evaluating the energy levels of its molecular orbitals. The experimental values may be used to check theoretical calculations of such energy levels. When a satisfactory correspondence has been achieved, theoretical approaches may facilitate assignment of the type and symmetry of the molecular orbital associated with each level.

The ionization potentials of molecules are several electron volts, even for the outermost valence electrons, and thus it is necessary to work in the UV region of the spectrum. Usually, the excitation source is a discharge through helium, which gives a band at 584 Å, corresponding to a photon energy 21.24 eV (UPS). If the electrons lie in the core of the molecule, more energy is

required to expel them, and in this case X rays, whose sources are chromium (5400 eV) and aluminum (1490 eV) (XPS), are employed. These core electrons are too tightly bound to be influenced by the outer valence electrons involved in bonding. They are thus characteristic of the individual atoms and provide information regarding the elements present (ESCA).

C. MASS SPECTROMETRIC TECHNIQUES

Interest in mass spectrometry as an experimental tool for investigating gas-phase, ion-molecule reactions is continually increasing. Particularly noteworthy features of this expansion are the recent introduction of productive experimental techniques, such as ion cyclotron resonance (71ARP527), high-pressure mass spectrometry (77ARP445), flowing afterglow methods (75MI1) and chemical ionization mass spectrometry (79MI2), specifically designed for precise measurements of thermodynamic and kinetic parameters of ionic processes in the gas phase. The first quantitative measurements carried out by these techniques were welcome insofar as they provided the needed means to separate intrinsic structural effects from solvation effects. However, most of the initial observations were so drastically unrelated to solution results that there developed among many chemists the feeling that the results were only curiosities peculiar to the gas phase and largely irrelevant to the area of solution chemistry.

This feeling underwent progressive changes in the last decade owing to a better understanding of the fundamental principles regulating gas-phase, ion-molecule reactions.

From correlations between gas-phase and solution stability data, it is now possible to obtain important information regarding intrinsic effects of molecular structure on reactivity (75MI2; 79MI3). Dramatic examples of reversals in acidity or basicity order in the gas phase and in solution can be readily rationalized in terms of specific bonding of solvent molecules to cations and anions.

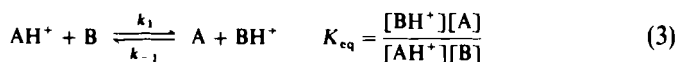
Now the feeling is undergoing a further change in that gas-phase thermodynamic measurements can be used with great utility as standards for the understanding of—and even in anticipating—major new advances of ion thermochemistry in solution.

1. *Ion Cyclotron Resonance Mass Spectrometry*

In ion cyclotron resonance spectrometry, a signal results when the cyclotron frequency of an ion, $\omega (=qH/mc)$, equals the frequency ω_0 of a marginal oscillator detector. At this point, the ions of a particular mass m and charge q are in resonance, and they absorb power from the marginal oscillator when the

magnetic field is fixed at H . The power absorbed is proportional to the number of ions and thus serves as a measure of ion intensity. The relative intensities of different ions in an ICR cell can be scanned in two ways. The first involves operating the marginal oscillator at constant frequency and varying the magnetic field. The cyclotron frequency of an ion is directly proportional to the magnetic field. As the magnetic field is varied, ions of different masses come into resonance. In the second method, the instrument is operated at a constant magnetic field and the frequency of the marginal oscillator is varied until it matches the cyclotron frequency of an ion.

This technique can be used to measure the equilibrium constant of a given proton transfer process [Eq. (3)].



It can be calculated simply from the peak area ratio $[\text{BH}^+]/[\text{AH}^+]$ and the pressure ratio $[\text{A}]/[\text{B}]$, which can be measured directly, e.g., by using a capacitance manometer.

Owing to the limitations on the total number of collisions (~ 100) currently attainable by the ICR technique, the largest equilibrium constants that can be reliably measured are less than 50, corresponding to ΔG° values of less than 2.0 kcal mol $^{-1}$ at 25°C. Occasionally, larger values of K_{eq} can be measured under particularly favorable circumstances, but these cases are unusual.

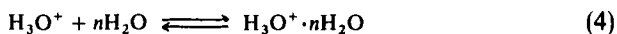
Because of the short residence time (~ 2 msec) of the ions in the drift cell of the spectrometer, the next major development of ICR technique was aimed at prolonging those times. Ion storage for periods of the order of seconds was achieved by the trapped-ion cell mode in ICR spectrometry (70MI2; 71JA4314; 72MI3). Even longer reaction times and a significant improvement in resolution were allowed by the development of Fourier-transform mass spectrometry (FT-ICR) (74CJC1997; 74CPL282; 74CPL489; 75JCP293).

An important feature of these approaches is the possibility of measuring reaction rates for proton transfer by ejecting one ion (e.g., AH^+) and observing the decay of the other ion (e.g., BH^+) (71IJM471; 76IJM63). Assuming that ion loss before ejection is negligible relative to that after ejection, the exponential decay of BH^+ is equal to the pseudo-first-order rate constant k_{-1} . Similarly, the rate constant k_1 can be measured by ejection of BH^+ . The equilibrium constants obtained from the ratio k_1/k_{-1} agree generally with those obtained from the ion intensity ratios in drift-cell experiments.

2. High-Pressure Mass Spectrometry

The first ion-molecule reactions studied in the gas phase under quasi-equilibrium conditions in a high-pressure mass spectrometer were

ion-clustering processes involving the gas-phase solvation of H_3O^+ [Eq. (4)] (63JCP1131).



The measurement of accurate equilibrium constants for these reactions provided valuable insight into the energetics of ionic solvation (72MI1; 77ARP445).

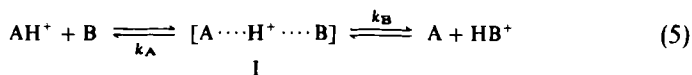
The method involves generation and reaction of ions in a field-free high-pressure region and diffusion of the ions through a small slit into a low-pressure region where they are accelerated and mass analyzed. A potential problem with this technique is that the need to sample the thermal reaction mixture for mass spectral analysis can lead to artifacts such as collisional decomposition of proton-bound dimers. However, such problems have been largely solved. The high-pressure mass spectrometric technique has the advantage, over the ICR techniques, of a large sensitivity range, making it possible to measure larger K_{eq} values. A better control of the gaseous reaction system is also possible, which makes estimates of the entropy variation of the process more reliable than by other techniques.

3. *Flowing Afterglow Techniques*

The flowing afterglow technique involves a fast helium flow at 0.5 torr in a reaction tube. Ions are generated by electron impact from gases introduced into the flow upstream from the filament. The ions generated can react with other neutrals introduced through nozzles downstream. The ions can be sampled through an orifice further downstream, which leads to a quadrupole mass filter. In this way, direct measurement of the forward and reverse rate constants of an equilibrium is attainable (69MI2; 73JCP6272; 75IJM151) and thus provides a measure of the equilibrium constant (73JA7512; 73JCP3504; 737PC61). The thermochemic quantities obtained by this technique are in good agreement with those measured by ICR mass spectrometry (75JCP1998).

4. *Chemical Ionization Mass Spectrometry*

Thermochemic parameters of gas-phase proton-transfer equilibria of type 5 are accessible in an experiment in which two neutral or charged bases, A and B, are bound by a proton and the resulting dimer ion I is dissociated (77JA1279; 81JA1313; 82IJM115; 83ARP187).



This procedure, based on the relative dissociation rates k_A and k_B , differs from the above methods. The present method employs a chemical ionization source and a mass filter. In the chemical ionization source, dimer ion I is produced by the action of a gaseous Brönsted acid on the A and B pair. A reverse-sector mass spectrometer, namely, a mass-analyzed ion kinetic energy spectrometer (MIKES) (73MI5), or a triple-quadrupole mass spectrometer (82IJM115), is used to select the dimer ion and to record the mass spectrum of its fragmentation products. The dissociation of I may be spontaneous, in the case that the dimer ion is metastable (MIKE spectrum), or it can be induced by a glancing collision with a gaseous target at kilovolt energy (MIKE/CID spectrum). The method is based on the assumption that, for similar species A and B, the competitive fragmentations of the dimer into the protonated monomers should have similar frequency factors (entropy changes). Furthermore, fragmentation of the dimer being simple cleavages, the reactions should have vanishingly small reverse activation energies (73MI2). If these conditions hold, the rates of fragmentations are controlled by the relative activation energies of each reaction channel, whose difference is equivalent to the free-energy change in the overall process indicated in Eq. (5) (Fig. 1). If secondary dissociations of ionic species from the reaction of Eq. (5) do not occur, then the relative abundances of the fragment ions from I will be determined by the rates of reactions shown in Eq. (5). Hence, the equilibrium constant for the reaction of Eq. (5) can be calculated from the relative peak heights of the fragment ions from dissociation of the proton-bound dimer I.

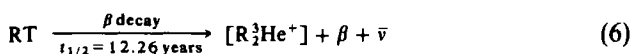
D. RADIOLYTIC AND NUCLEAR METHODS

The mechanistic aspects of gas-phase, ion-molecule reactions have received a great deal of attention even though to a minor extent with respect to equilibrium studies (75MI3; 76MI1; 79MI4). The main reason for this situation is found in the inherent limitations of mass spectrometric approaches, which provide only partial and largely indirect information regarding certain basic features of ion-molecule reactions, such as their intramolecular selectivity, orientation, stereochemistry, steric effects, structure, and isomeric composition of the ionic reactants and products. This information is generally accessible in solution-chemistry studies. The inherent inadequacy of purely mass-spectrometric approaches to mechanistic investigation of gas-phase heteroaromatic chemistry is manifested by the rarity of pertinent unambiguous data and by the growing interest in alternative experimental approaches, such as gas-phase radiolysis (66ARP205; 69MI3;

73MI3; 75MI4; 79MI5; 82MI2) and nuclear-decay (70APO79; 75MI5; 82MI2; 83G37) techniques, specifically designed to extend the classical methodology of physical organic chemistry to gas-phase, ionic processes.

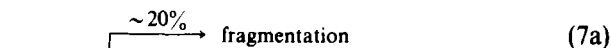
The radiolytic technique is based on the generation of unsolvated ions by the passage of high-energy electromagnetic radiation (X or γ rays) through the gaseous system (66ARP205; 69MI3; 73MI3; 75MI4; 79MI5; 82MI2). High-energy quanta lose energy to the medium through photoelectric and Compton effects, or via pair-production processes, which ultimately result in the release of energetic (up to hundreds of eV) electrons, responsible for more than 99% of the ionization and excitation events in the irradiated gas. The fate of the reactive species formed (ions, electrons, radicals, and excited molecules) can be controlled to a certain extent by the composition of the irradiated system. Thus excited species can be made to lose their excess energy via many unreactive collisions with certain components of the gaseous system. Thus their thermalization takes place prior to reaction with the neutral substrate of interest present in the gas at very low concentrations. Undesired radical reactions can be efficiently suppressed by appropriate radical scavengers, which nevertheless must be inert toward the ionic species investigated. The actual isolation of the neutral products from the ionic processes occurring in the irradiated mixture and the determination of their structure and isomeric composition, in terms of the experimental conditions, provide useful and otherwise inaccessible information regarding the gas-phase reactivity of the neutral compounds investigated toward the radiolytically formed ionic reactants.

An alternative method for producing known amounts of an ionic reactant of precisely defined structure in the presence of an organic compound is based on the spontaneous decay of a tritium atom covalently bound in an appropriate precursor (70APO79; 75MI5; 82MI2; 83G37). In the specific case of a tritiated molecule RT, the nuclear transition of the ^3H (T) atom gives a stable ^3He daughter (via emission of an antineutrino and a β particle) whose energy ranges up to ~ 18 keV, with a mean value of 5.6 keV [Eq. (6)]. The chemical consequences of the β decay arise in part from the excitation of the daughter species because of the momentum imparted to the ^3He moiety following emission of the β and $\bar{\nu}$ particles and the perturbation ("shaking") of the electron cloud after the sudden increase of the nuclear charge (65MI1).



Theoretical treatments predict and sophisticated mass-spectrometric experiments confirm that such recoil and electronic excitation sources may cause fragmentation and multiple ionization only in a small fraction of the primary decay species [Eq. (7a)], whereas the remainder ($\sim 80\%$) is formed in the

ground state, with negligible recoil and excitation energy [Eq. (7b)].



The most significant chemical consequence of the tritium β decay can be traced simply to the sudden change in chemical identity that is undergone by the tritium atom. This affects all of its properties, including the ability to remain bonded to the rest of the molecule. Thus while the $\text{T}\frac{3}{2}\text{He}^+$ ion, formed from the decay of a T_2 molecule, is quite stable and survives dissociation (relative yield $\geq 90\%$) (59MI1), the repulsive nature of the $\text{C}-\frac{3}{2}\text{He}$ interaction following the decay of a tritiated hydrocarbon (e.g., methane, $\text{R} = \text{CH}_3$), causes immediate dissociation (relative yield of CH_3^+ , 82%) (58JPC1377). The $\frac{3}{2}\text{He}$ fragment shows up as a neutral atom and leaves a positive charge on the organic fragment R . This is due to the considerably higher ionization potential of $\frac{3}{2}\text{He}$ with respect to those of all organic radicals.

By this approach, a variety of tritiated positive ions have been generated under largely different experimental condition, i.e., from a dilute gas state to dense gases and to liquids. The reactivity properties of such ions toward organic substrates have been evaluated by an extension of the mechanistic and kinetic tools typical of classical solution-chemistry studies.

III. Molecular Properties and Reactivity

A. SIX-MEMBERED HETEROAROMATIC RINGS

Reactivity at the ring atoms in six-membered heteroaromatic compounds is generally quite predictable on the basis of a variety of reactivity indices such as net atomic charges, π charges, π -electron densities, or localization energies. All of these theoretical parameters qualitatively agree with most accepted empirical concepts about electronic (mesomeric, inductive) and steric effects of substituent groups derived from linear free-energy relationships in solution studies. Figure 2 shows the most favored positions of attack of electrophilic and nucleophilic species toward simple azines, as predicted by the above reactivity indices and observed in solution. Reactivity indices predict the ring-nitrogen atoms of such π -deficient heteroaromatic rings as the most attractive sites for electrophiles. It follows that electrophilic attack at the ring carbons is an exceptionally difficult process in solution. Under the conditions necessary for electrophilic substitution in solution, the azine is almost quantitatively

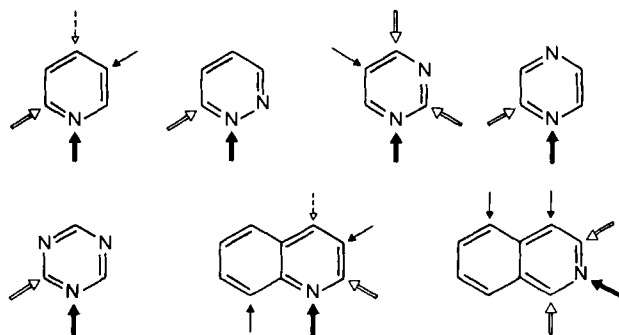


FIG. 2. Positional selectivity in substitution reactions of azines. Black arrows: electrophilic substitutions; white arrows: nucleophilic substitutions. Dashed and solid light arrows refer to second best positions for nucleophilic and electrophilic attack, respectively.

converted to the ammonium salt, which is obviously less prone than the free base to undergo electrophilic attack at its carbon atoms. A comparison between the reactivity indices calculated for both pyridine and pyridinium ion (Fig. 3) accounts for the poor reactivity of the carbon atoms of azines, which is observed in solution under electrophilic conditions. These effects also apply to the benzo analogs of azines where electrophilic attack takes place preferentially at the carbon atoms of the benzo-fused ring.

Six-membered heteroaromatic rings have received a great deal of attention from theoretical and experimental standpoints. In particular, the molecular orbital energy levels and the frontier electron densities of these compounds have been evaluated. Figure 4 shows the energy levels of the first five

		Net Total	π	π -Electron
		Charge	Charge	Density
	C-3	-.04	+.04	.95
	C-2	-.09	-.03	1.00
	C-1	-.02	+.02	.92
	N	-.06	-.04	1.19
	C-3	+.04	+.19	.83
	C-2	-.08	-.02	1.01
	C-1	+.05	+.10	.76
	N	+.02	-.35	1.62

FIG. 3. Reactivity indices of pyridine and pyridinium ion [74ACS(A)315].

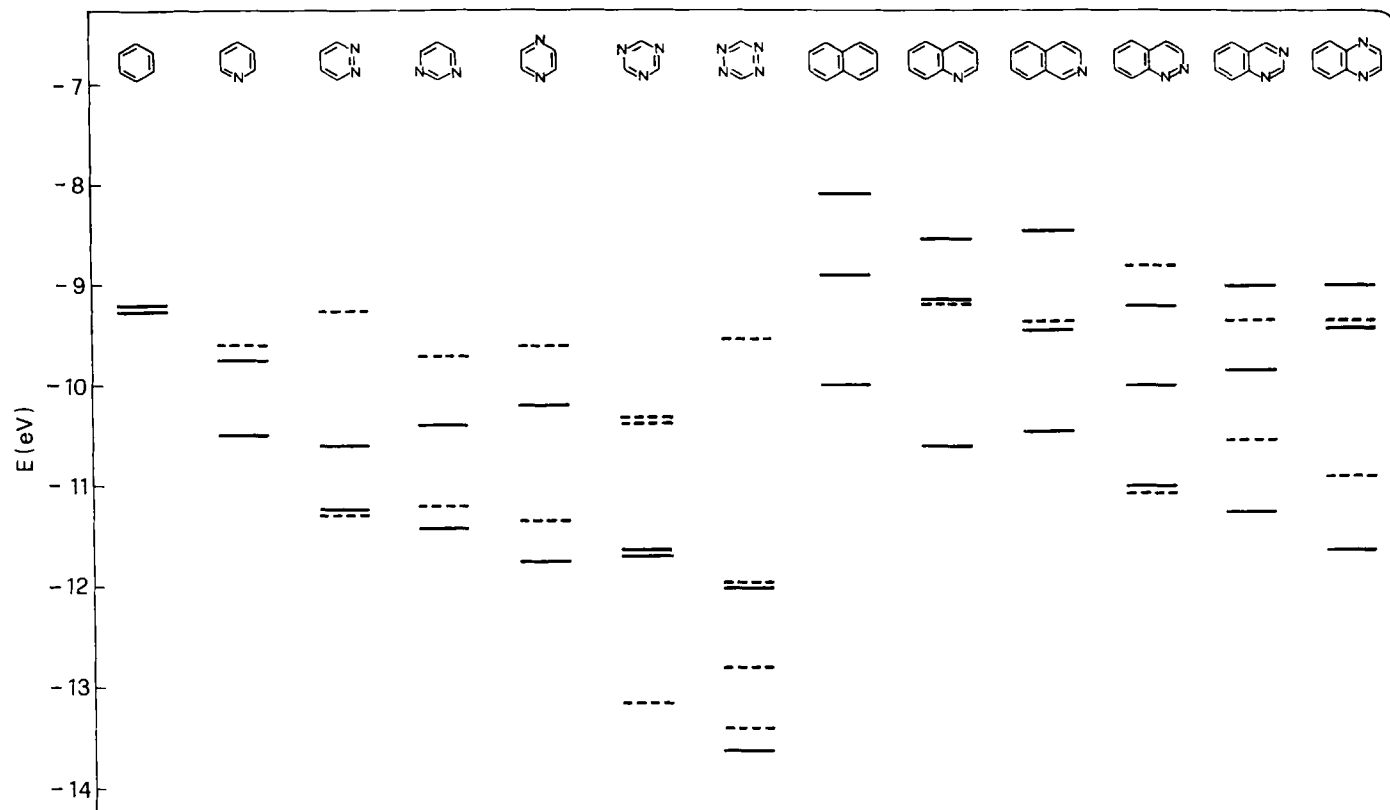


FIG. 4. Orbital energy levels of azines. Solid lines: π orbitals; broken lines: lone-pair orbitals (72HCA255; 72HCA274).

photoelectron spectroscopic bands of azines in the interval of energies between 8 and 15 eV (72HCA255; 72HCA274; 78BCJ3482).

A satisfactory agreement is generally observed between the calculated energy levels of azines and those experimentally derived from photoelectron spectroscopy (68JCP953; 72HCA255; 72HCA274; 72JCS(D)564; 78BCJ3482; 79CP113). A symptom of this correspondence is provided by the data in Table I, which show the theoretical and experimental ionization potentials of simple azines (74PMH1; 78MI2). Theoretical description of the lone-pair, nonbonding orbitals of azine provides a tool for determining their frontier electron densities (Fig. 5). A qualitative agreement between the reactivity indices of Fig. 2 and the frontier electron density distribution of Fig. 5 is evident. This accounts for the reasonable qualitative correspondence between the reactivity pattern of azines, observed in solution, and theoretical predictions.

B. FIVE-MEMBERED HETEROAROMATIC RINGS

Numerous attempts have been made to explain on a theoretical basis the reactivity properties of five-membered heteroaromatic rings (61MI1; 68MI1; 69MI1; 70ACR217; 70MI1; 71PMH55; 74MI1; 75CB97; 75PAC767; 77MI1; 78CB396; 78MI1; 79MI1). Figure 6 shows a representation of the reactivity indices for several five-membered heteroaromatics. Different conclusions can be drawn from their application in predicting reactivity properties of these compounds.

A long-standing difficulty of most semiempirical molecular orbital calculations (HMO, EHT, PPP, CNDO, INDO, MINDO, etc.) has been the

TABLE I
CALCULATED AND EXPERIMENTAL ENERGY LEVELS IN PYRIDINES
AND RELATED AROMATIC COMPOUNDS

Compound	<i>IP</i> (experimental)	<i>IP</i> (calculated)
Pyridine	9.73	9.68
	10.50	10.43
Benzene	9.24	9.16
	10.61	10.57
Pyridazine	11.30	11.32
	10.41	10.57
Pyrimidine	11.39	11.32
	10.18	10.19
Pyrazine	11.77	11.70

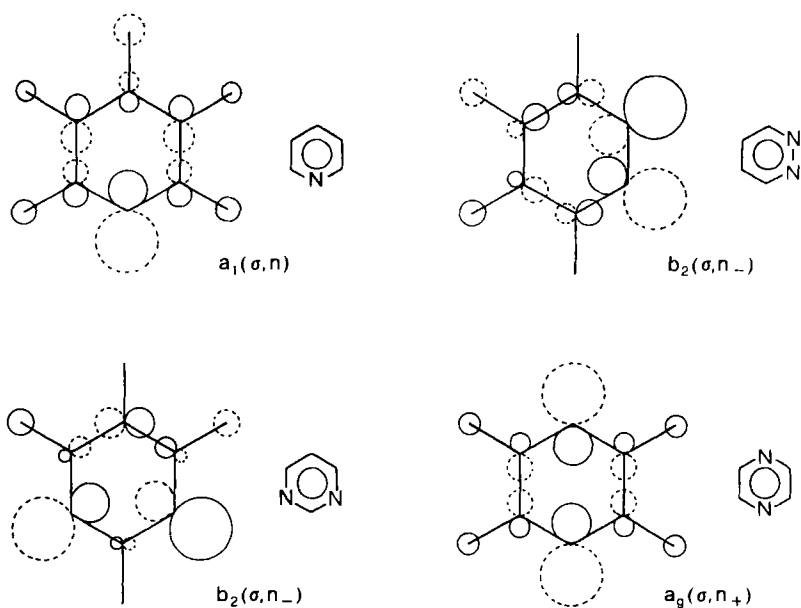


FIG. 5. Schematic representations of the HOMO of azines (72HCA255).

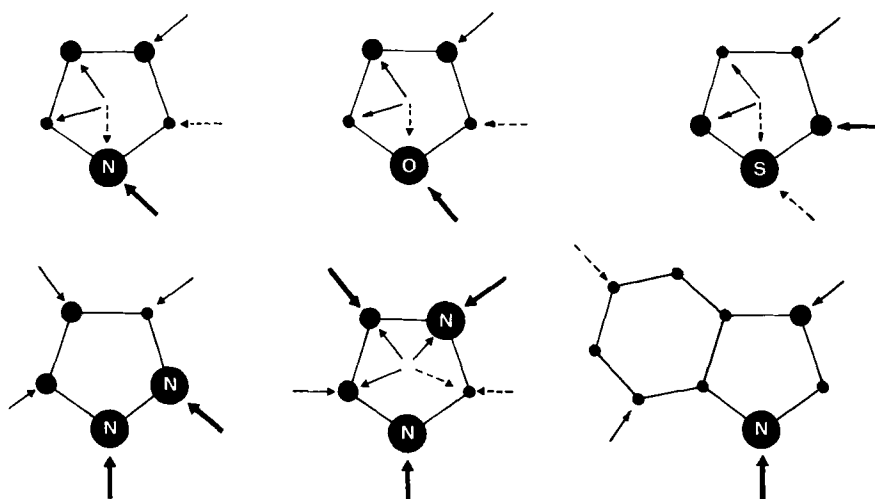


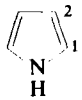

FIG. 6. Schematic representations of reactivity indices of simple five-membered heteroaromatic compounds. Full circles, π -electron densities; internal arrows, π charges; external arrows, net charges; heavy solid arrows, first highest charge densities; light solid arrows, second highest charge densities; dashed arrows, third highest charge densities.

assignment of parameters for both Coulombic and resonance integral terms concerning the heteroatom, which, in these π -excessive heterocycles, contributes to their aromaticity with an electron pair. The problem cannot be completely solved by reference to values obtained for model compounds because the parameters are themselves altered when the environment changes [72T3657; 72ZOR404; 74ACS(A)315; 76DIS(B)3907]. All too often parametric equations are chosen in such a way that reasonable results for any selected molecular or reactivity properties can be made. The use of *ab initio* techniques does not remove all difficulties. In general, these calculations, which do not involve in principle the plethora of arbitrary parameters typical of semiempirical methods, provide reasonable estimates of a variety of molecular properties in qualitative agreement with those of most refined semiempirical calculations (MINDO/3, MNDO, etc.). However, the agreement with accessible experimental data is rarely satisfactory (71TCA52; 72TCA357; 79NJC473), as well as the agreement between different *ab initio* estimates of the same molecular property [73CPL305; 73MI6; 74JCS(P2)1893; 74TCA279; 74ZN(A)624; 76JA4361; 76JCS(P2)81; 78JA1371; 81JST163; 81JST249]. As far as the reactivity indices are concerned, the relevant estimates are never quantitatively similar and, in some instances, appear qualitatively discordant, as testified by the π densities of the α and β positions of the heteroaromatics of Table II. The conditions for an effective comparison of the calculated reactivity indices of Table II and Fig. 6 with the reactivity pattern commonly observed for five-membered heteroaromatics in solution appear rather precarious. To make matters worse, it should be taken into account that the reaction environment of some substitution reactions in solution may profoundly modify the electronic properties of the heteroaromatic substrate. For instance, under acidic conditions electrophilic substitutions on imidazole, pyrazole, etc., may well occur on the conjugate acid of the substrate (65JCS1051). By contrast, under alkaline conditions nucleophilic substitutions on pyrrole, imidazole, etc., may involve the conjugate base of the substrate (53JCS3937; 67MI1).

The geometry and the electron properties of such charged intermediates are expected to be profoundly different from those of neutral precursors (Fig. 7) (68JA4232). Therefore, the already ambiguous scenario offered by theoretical predictions of heteroaromatic reactivity appears further complicated by the concomitant presence of these conjugate species in the reaction medium (67T2513).

The He(1 α) photoelectron spectra of the parent five-membered heteroaromatic molecules have undergone an exhaustive study. In the beginning, the assignment of the ionization energies to appropriate occupied molecular orbitals was confused by the unexpected reversal in the sequence of the two highest MOs in tellurophene relative to the other parent heterocycles. The

TABLE II
SEMIEMPIRICAL AND *Ab Initio* ESTIMATES OF THE π -ELECTRON DENSITIES
OF PYRROLE AND FURAN

								
	C-2	C-1	N	C-2	C-1	O	Source	
Semiempirical								
(PPP)	1.0261	1.0222	1.9035	(PPP)	1.0236	1.0081	1.9365	<i>a</i>
(PPP)	1.0678	1.0760	1.7125	(PPP)	1.0671	1.0487	1.7683	<i>b</i>
(EHT)	1.13	1.08	1.58	—	—	—	—	<i>c</i>
(MINDO/2)	1.1016	1.0432	1.7105	—	—	—	—	<i>d</i>
(CNDO/2)	1.0854	1.0848	1.6553	—	—	—	—	<i>e</i>
<i>Ab Initio</i>								
	—	—	—	1.079	1.045	1.753	—	<i>f</i>
	—	—	—	1.067	1.078	1.710	—	<i>g</i>
	1.10	1.07	1.65	1.08	1.04	1.76	—	<i>h</i>
	1.0752	1.0953	1.6589	—	—	—	—	<i>i</i>

^a R. L. Flurry, Jr., E. W. Stout, and J. J. Bell, *Theor. Chim. Acta* **8**, 203 (1967).

^b S. Katagiri and C. Sandorfy, *Theor. Chim. Acta* **4**, 203 (1966).

^c W. Adam, A. Grimison, and G. Rodriguez, *Tetrahedron* **23**, 2513 (1967).

^d J. T. Gleghorn, *J. C. S., Perkin Trans. 2*, 479 (1972).

^e D. T. Clark, *Tetrahedron* **24**, 4689 (1968).

^f T. K. Ha, *J. Mol. Struct.* **51**, 87 (1979).

^g I. G. John and L. Radom, *J. Am. Chem. Soc.* **100**, 3981 (1978).

^h F. R. Cordell and J. E. Boggs, *J. Mol. Struct.* **85**, 163 (1981).

ⁱ E. Clementi, H. Clementi, and D. R. Devis, *J. Chem. Phys.* **46**, 4725 (1967).

reported values are compared in Fig. 8 [69IJM471; 76JCS(P2)276; 79CPL355]. The assignments are based on comparison with the spectra of reduced heterocycles, the effect of ring substituents and comparisons with results of molecular orbital calculations. The energy of the first HOMO ($\pi 1a_2$), which extends exclusively over the carbocyclic part of the molecules, is almost constant for the parent heteroaromatics, whereas the second HOMO ($\pi 2b_1$) energy depends markedly on the heteroatom and increases as the electronegativity decreases.

The first and second HOMO electron densities of parent five-membered heteroaromatics may be directly evaluated from theoretical calculations and are illustrated qualitatively at the left side of Fig. 8. A distinct preference for the α carbons of parent heteroaromatics is therefore predicted for electrophilic species, whose reactivity is regulated by preliminary charge-transfer interactions with the substrate (76JA4361). In an abundant number of cases, predominant α substitution in simple five-membered heteroaromatics is

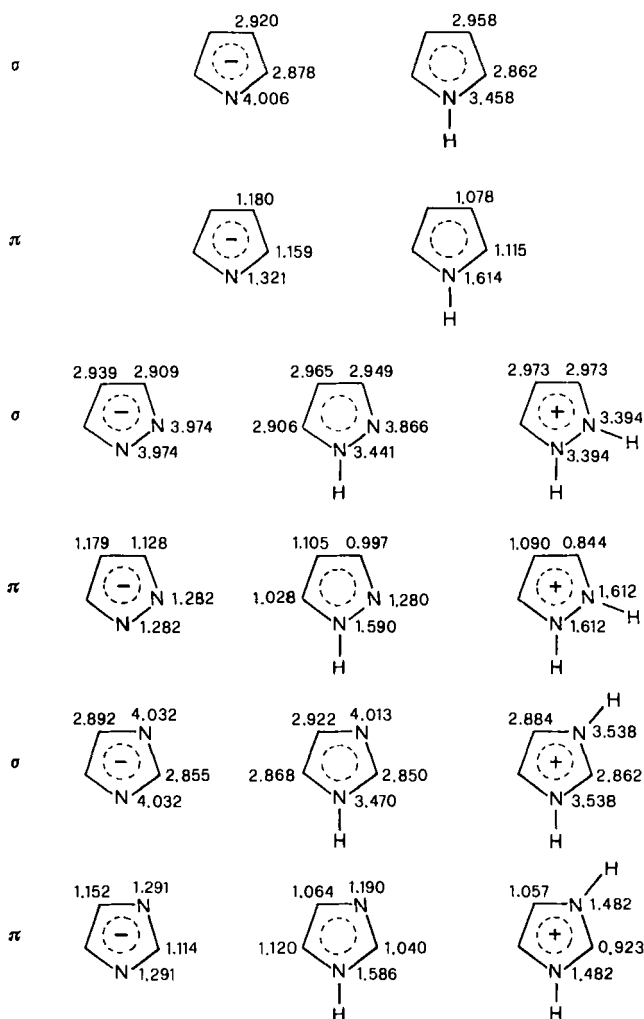


FIG. 7. Charge densities of representative five-membered heteroaromatic compounds and of their conjugate acids and bases (68JA4232).

normally met in solution chemistry (68 MI2; 71AHC235); this agrees well with predictions based on frontier electron densities. However, it is in qualitative disagreement with most of the other reactivity indices (net atomic charges, π densities, etc.; see Fig. 7 and Table II) calculated for this class of compounds.

The available localization energies for electrophilic substitution on the parent five-membered heteroaromatics correctly predict orientation for substitutions in solution ($\alpha > \beta$), but are much less satisfactory for the benzo

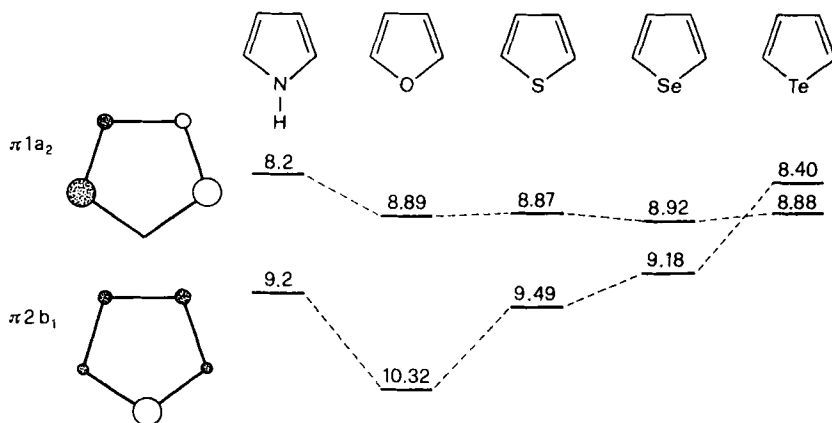


FIG. 8. Vertical ionization energies (eV) of the molecular π orbitals of parent five-membered heteroaromatic compounds [76JCS(P2)276].

derivatives (Fig. 9) [59AJC152; 72JCS(P2)479]. However, as with π -electron densities, the calculations of localization energies by molecular orbital theory is subject to some uncertainty because of the difficulty in deciding on the value of the auxiliary inductive parameter.

While correlation between the localization energies and the orientation of substitution is partially satisfactory, their correlation with relative rates of substitution in solution is very poor. Calculated differences in localization energies of a few kilocalories per mol can hardly explain the differences of many orders of magnitude between the corresponding partial rate factors measured for substitution reactions in solution. In some instances, this large discrepancy is ascribed to preliminary ionization of the neutral substrate (e.g., the imidazolium ion), which establishes significant electrostatic repulsion between the ionic reactants. In other cases, where this effect is less clear, the conventional calculation of localization energies appears grossly to underestimate the effect of the heteroatom in the aromatic system and the consequence on the electron distribution on the ring by its interaction with the environment.

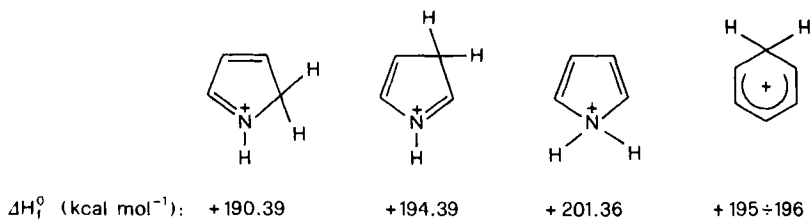


FIG. 9. MINDO/2 calculations of protonated forms of pyrrole [72JCS(P2)479].

Molecular electrostatic potential has been used in predicting the protonation sites and relative tendencies toward protonation in many organic molecules, including heteroaromatic compounds (72CPL622; 73CC617; 73MI1; 75CPL441).

A detailed analysis of the various contributions to the interaction between a point charge and an isolated molecule indicates that the electrostatic effect is only one major factor involved in the interaction. Other factors, such as polarization and charge transfer, have roles as well (72CPL29; 73MI1; 75CPL441). In many cases, however, these other factors seem partially to cancel each other, and their net effect is not sufficient to outweigh the electrostatic contribution.

The molecular electrostatic potentials, computed from CNDO/2 (73CC617), INDO (75T915) and *ab initio* (78T275) wave functions, concerning parent five-membered heteroaromatics are shown in Figs. 10a–g. Ground-state furan presents a single region of negative potential (attractive to an electrophile) extended over the oxygen atom. There are no negative potentials near either the α or the β positions (Fig. 10a). When the potential is computed

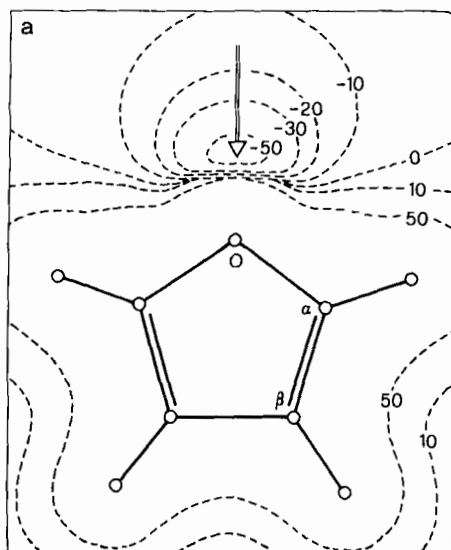


FIG. 10. Electrostatic potential in (a) the molecular plane of furan, (b) the molecular plane of furan with its α hydrogen bent below the plane, (c) the molecular plane of pyrrole, (d) the molecular plane of *N*-methylpyrrole, (e) perpendicular planes through the α and β carbons of pyrrole, (f) a plane 1.5 au above the molecular plane of pyrrole with the H on N bent below the molecular plane, (g) a plane 1.5 au above the molecular plane of pyrrole with the hydrogens on N and C_α both bent below the molecular plane (75T915).

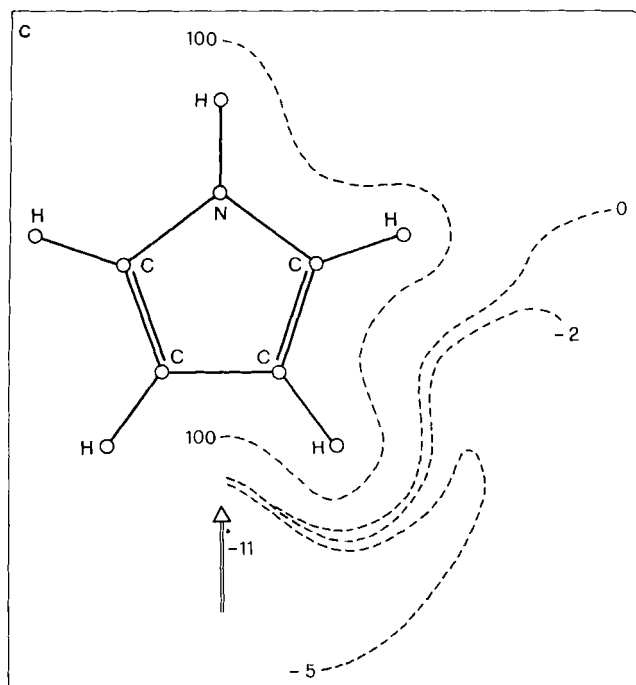
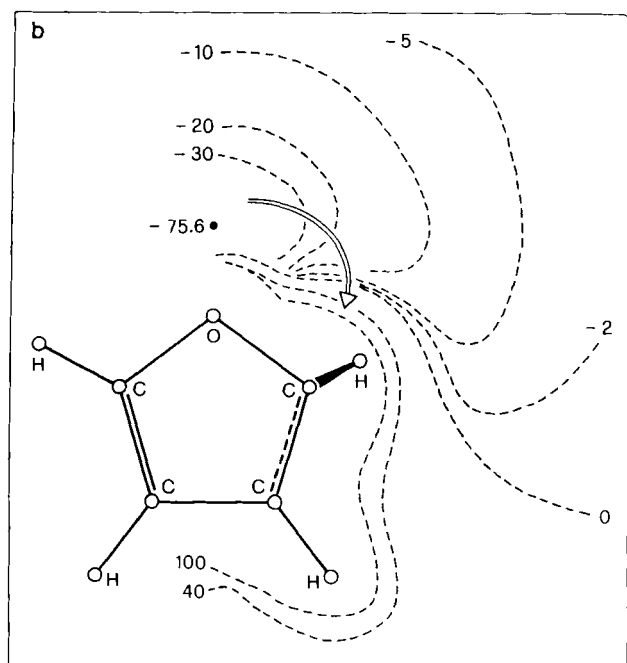


FIG. 10 (continued).

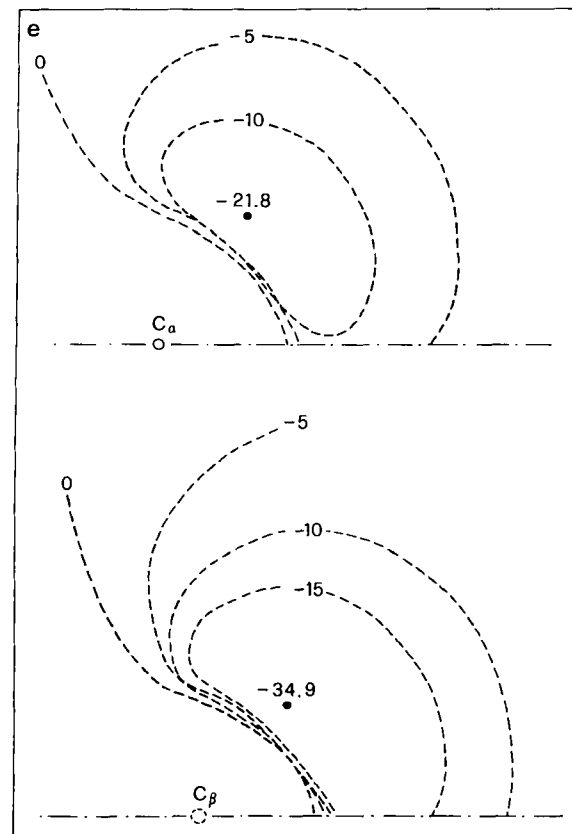
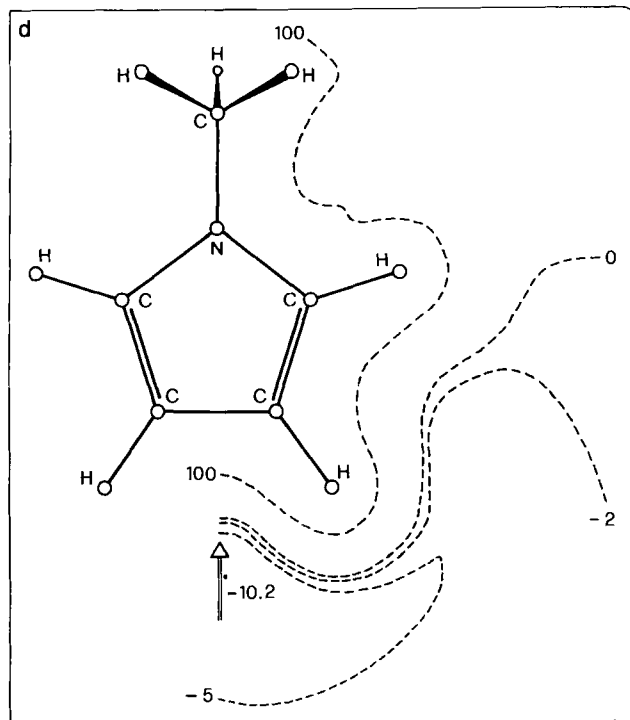


FIG. 10 (continued). See legend on p. 22.

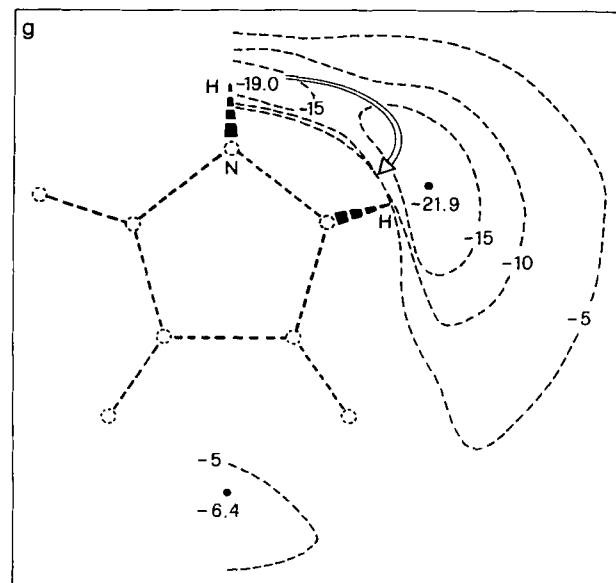
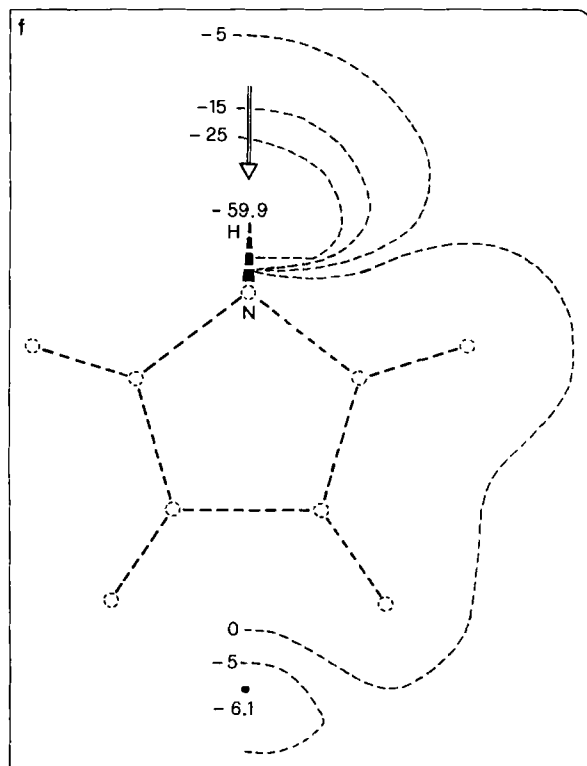


FIG. 10 (continued). See legend on p. 22.

for the two hypothetical structures having a C_α —H or a C_β —H bond bent out of the molecular plane, a very definite attractive region develops over the corresponding carbon atom (Fig. 10b). It was suggested (73CC617), therefore, that electrophilic attack on furan is preceded by the movement of a hydrogen atom out of the plane of the molecule, which produces a path of negative potential leading to the carbon atom involved. This path turns out to be roughly equally attractive toward an approaching electrophile regardless of whether it is the α or the β hydrogen that is moved out of the plane. Consequently, this factor alone would not suffice to explain the preference for α substitution, normally observed in solution. The key difference is that the attractive region which results from bending the α hydrogen is part of the extensive negative potential near the oxygen atom, whereas when the β hydrogen is bent, there remains an intervening positive potential between the two negative regions. Accordingly, an electrophile that approaches the very attractive region near the oxygen can fairly easily migrate to the α carbon since there is no positive barrier, while an analogous migration to the β carbon is hindered. Thus substitution in furan can apparently result from an initial approach to either the α carbon or the oxygen, whereas β substitution seems to require a direct attack upon the β carbon. It is to be expected, therefore, that α substitution will occur with a much greater frequency, as indeed is found to be the case in solution.

However, it is not clear why the same arguments do not apply in nucleophilic substitutions in furans, where reports of displacements in solution from the 3 position are rare and where the reactivity of five-membered heteroaromatics is many orders of magnitude higher than that of benzene.

The analysis of the reactivity properties of pyrrole and *N*-methylpyrrole presents somewhat greater problems than that for furan. Figures 10c and 10d show the electrostatic potentials in the planes of these molecules. In contrast to furan, there are no in-plane regions of negative potential near the heteroatoms. This is because of the hydrogen or methyl substituent on the nitrogen; hydrogen atoms generally have positive potentials associated with them. The only negative regions in pyrroles are outside of the C_β — C_β bonds. Thus as in the case of furan, the ground-state potentials provide no basis for predicting a preference for α substitution; if anything, they suggest that the β positions might be more vulnerable to electrophiles. Even out-of-plane bending of a single C—H bond of pyrroles does not modify this prediction since the so-developed negative potential is distinctly more attractive for the β carbons than for the α (Fig. 10e). In order to make the α carbons of pyrroles the most likely site for electrophilic attack, combined C_α —H and N—H (or N—CH₃) bendings out of the molecular plane have been invoked. The low force constant and the low energy involved in the bending of the N—H (or N—CH₃) bonds indicate that the H (or CH₃) will be out of the plane most of the

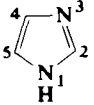
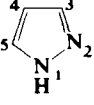
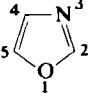
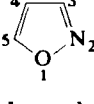
time. This bending creates an attractive region around the heteroatom, thus reproducing a situation similar to that of ground-state furan (Fig. 10f). Additional bending of the C_2-H bonds further extends this attractive region to the α carbons (Fig. 10g).

Certainly, this interpretation is open to the same questions raised in the case of furan. Furthermore, it is not clear why the easy bending of the $N-H$ (or $N-CH_3$) bonds does not favor electrophilic displacement at the N atom—an extremely rare process under electrophilic conditions.

The values of the electrostatic molecular potential $V(\bar{r})$ in some characteristic regions of simple heteroaromatics are given in Table III (72TCA101).

The restrictive approximations of the molecular electrostatic potential approach make the relevant theoretical predictions on heteroaromatic

TABLE III
VALUES OF THE ELECTROSTATIC MOLECULAR
POTENTIAL $V(\bar{r})$ IN SOME CHARACTERISTIC
REGIONS

Molecule	Position	$V(\bar{r})^a$
 Imidazole	C-2—H	− 5.0
	C-4—H	− 15.1
	C-5—H	− 7.5
	N-1—H	0
	N-3	− 82.0
 Pyrazole	C-3—H	− 13.6
	C-4—H	− 16.7
	C-5—H	− 7.5
	N-1—H	− 2.0
	N-2	− 74.0
 Oxazole	C-2—H	+ 5.0
	C-4—H	− 3.6
	C-5—H	+ 2.0
	O-1	− 31.2
	N-3	− 68.4
 Isoxazole	C-3—H	− 1.8
	C-4—H	− 2.8
	C-5—H	+ 2.0
	O-1	− 37.0
	N-2	− 66.8

^a All $V(\bar{r})$ values are expressed in kcal/mol. The values in bold face refer to ring plane points; the other to points 2 Å above the ring plane. (72TCA101).

reactivity hardly more significant than those based on the traditional static reactivity indices considered above. However, the electrostatic potential method emphasizes the need for a consideration of the dynamic components of reactivity that reflect the changes occurring in the electronic structure of the reactants at each stage of the interaction. Without any doubt, in order to be applied to predicting solution-phase reactivity, the method should take into due consideration the perturbation mediated by the solvent molecules.

The potential surface of a few protonated heteroaromatics, such as pyrrole or furan, has been analyzed for minima and saddle points of first and second order by semiempirical methods. The pyrrole data are given in Fig. 11

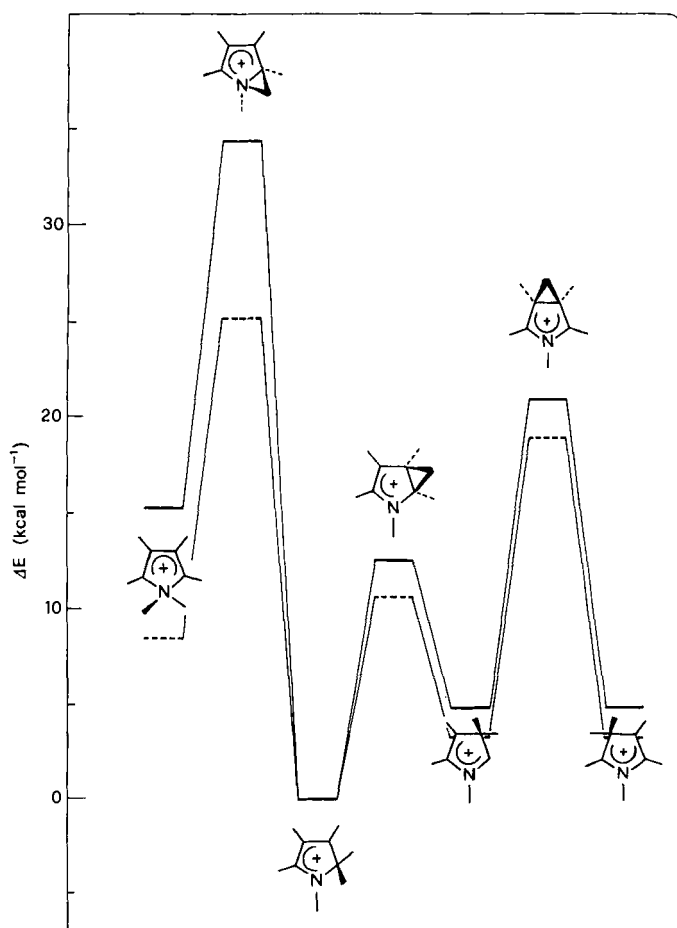


FIG. 11. CNDO/2 (solid lines) and MINDO/2 (broken lines) calculations of the energy levels of protonated pyrrole (80JPR147).

(77TL3565; 80JPR147). Local energy minima correspond to isomeric σ -protonated pyrroles, whose stability has been computed and found to decrease in the $\sigma_\alpha > \sigma_\beta > \sigma_N$ order. The energy gaps between the minima are in satisfactory agreement with other semiempirical calculations of the localization energies of protonated pyrroles (Fig. 9). Analysis of the energy profile (Fig. 11) linking the local minima (σ complexes) indicates that hydrogen-bridged structures correspond to energy saddle points, representing the activation barriers for hydrogen shifts in the protonated pyrrole intermediates. The face-protonated (π complex) pyrrole structure, whose computed stability is lower than that of the corresponding benzene structure, corresponds to a local energy maximum.

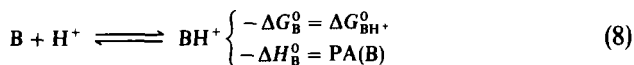
The appreciable barrier calculated for the H shift from the N-protonated pyrrole to the α -protonated structure appears to be in striking contrast with the easy $N \rightarrow C_\alpha$ migration that is predicted by the molecular electrostatic potential method.

While the relative stability of the σ complexes may be related to the positional basicity of pyrrole, no precise prediction on orientation in the proton attack on pyrrole may be advanced on the grounds of the calculated potential-energy surface of protonated pyrrole. Positional selectivity in the electrophilic attack on pyrrole is, in fact, regulated by the transition-state energy developed in the intermolecular interaction between pyrrole and the external charged electrophile. Owing to the very high degree of complexity involved, theoretical calculations of such energy profiles are at their very early stage.

IV. Thermodynamics

A. ACIDITY AND BASICITY IN THE GAS PHASE

The gas-phase basicity of a neutral or charged base B is defined as the negative of the free-energy change for the proton-transfer reaction of Eq. (8) ($-\Delta G_B^0$), while the proton affinity (PA) is the negative of the corresponding enthalpy change ($-\Delta H_B^0$). The free-energy change of the process in Eq. (8) is defined as the gas-phase acidity of the (charged or neutral, respectively) conjugate acid of the base ($\Delta G_{BH^+}^0$).



Thus the direction of the proton-transfer reaction of Eq. (3) gives the relative gas-phase basicities of bases A and B [$\delta\Delta G^0 = \Delta G_A^0 - \Delta G_B^0$; $\delta\Delta H^0 = PA(B) - PA(A)$] or acidities of their conjugated acids AH^+ and BH^+

($\delta\Delta G^0 = \Delta G_{\text{AH}^+}^0 - \Delta G_{\text{BH}^+}^0$). It has been usually assumed that these free energies differ from enthalpies for proton transfer by a $T\Delta S^0$ term approximately equal to that calculable from the symmetry changes in the reaction. Thus the ΔG and PA values differ by the entropy term calculated for a free proton by the Sackur–Tetrode equation ($7.75 \text{ kcal mol}^{-1}$) and by the entropy term because of symmetry changes expressed in Eq. (9).

$$T\Delta S_{\text{sym}}^0 = RT \ln(\sigma_{\text{BH}^+}/\sigma_{\text{B}}) \quad (9)$$

In a few cases, these entropy terms have been determined by measuring equilibrium constants over a wide range of temperatures, using a variable-temperature, high-pressure mass spectrometer (73JA3504) and variable-temperature ion cyclotron resonance drift and trapped-ion cells (78MI3). In such measurements, the entropy terms for proton-transfer reactions have been very small and about equal to the calculated ones, except in cases where intramolecular hydrogen bonds are formed. Generally, gas-phase acidity and basicity measurements have been made at only one temperature, and the entropy term has been calculated to give reported proton affinity values.

A number of proton-transfer equilibrium constants for reactions similar to those shown in Eq. (3) have been measured by ion cyclotron resonance, high-pressure mass spectroscopy, flowing afterglow, MIKES, and MIKES/CID techniques. These studies allowed the relative proton affinities of a variety of bases to be determined with an accuracy of better than $\pm 0.2 \text{ kcal mol}^{-1}$ and compared with related thermodynamic data measured in solution.

In one of the first such studies carried out by high-pressure mass spectrometry, Munson was able to show that the gas-phase basicities of methyl-substituted amines increased regularly with increasing methyl substitution (65JA2332). Similar results were obtained for other organic bases in the gas phase by using ion cyclotron resonance techniques (68JA5636; 68JCP1783; 71JA3914; 76JA311). The solution basicities of alkylamines follow, instead, an irregular order, namely, $\text{NH}_3 < \text{Me}_3\text{N} < \text{MeNH}_2 < \text{Me}_2\text{NH}$ (65MI2).

Similar results were obtained by Brauman and coworkers on the basicities of alkylamines and acidities of aliphatic alcohols (68JA5636; 71JA3914). These observations indicated immediately that such gas-phase data supply a set of intrinsic basicities and acidities that could be used to clarify our understanding of the origin of solution-phase basicity and acidity orders (72JA4724; 72JA4726; 72JA4728; 76JA318). On these grounds, a number of intrinsic effects of molecular structure on basicity and acidity have been identified, which allowed understanding of specific solvation phenomena in those cases where a dramatic alteration, or even a reversal, of the basicity or acidity order in the gas phase and solution was observed.

B. STRUCTURAL EFFECTS ON ACID-BASE EQUILIBRIA

1. *Site of Protonation*

Thermochemic quantities measured for acid-base equilibria, both in solution and in the gas phase, generally indicate a marked effect of the atomic site of protonation on the base strength (77JA5417). Proton affinities and related quantities of nitrogen and oxygen bases show large changes as a result of hybridization changes at N and O (75JA4136). An increase in the lone-pair *s* character results in substantial decrease in PA and larger increases in the lone-pair ionization potentials (Table IV).

Neither of the mass-spectrometry methods commonly used for measuring gas-phase basicities is capable of directly identifying the site of protonation in the base molecule, and those methods traditionally employed to deduce this information (e.g., NMR spectroscopy) are carried out in solution, in which the

TABLE IV
GAS-PHASE BASICITIES, PROTON AFFINITIES, AND ADIABATIC AND VERTICAL
IONIZATION POTENTIALS OF COMPOUNDS OF N, O, P, AND S WITH
VARIOUS HYBRIDIZATIONS AT 25°C^a

	GB	PA	aIP	vIP	<i>s</i> (%) ^b
Aziridine	207.5	215.7	214	226.7	30
Me ₂ NH	212.3	220.5	188	205.9	25
Azetidine	214.5	222.7	191	206.6	26
Piperidine	217.2	225.4	181	199.7	25
Pyridine	212.6	220.4	—	223.7	33
MeCH=NEt	215.0	222.8	204	217.7	33
Manxine	223	231	160	161.7	0
MeCN	183.1	190.9	—	303.0	50
Oxirane	182.3	189.6	240	243.5	30
Me ₂ O	185.8	193.1	226	232.9	25
Oxetane	189.6	196.9	221	223.0	26
CH ₂ O	169.9	177.2	—	250.9	33
MeCHO	181.1	188.9	—	235.4	33
Me ₂ CO	189.9	197.2	—	223.9	33
Thiirane	188.5	195.8	206	208.2	30
Me ₂ S	193.4	200.7	198	200.2	29
Thietane	194.0	201.3	196	198.8	26
Phosphirane	187.6	194.8	216	224.8	30
Me ₂ PH	208.9	217.1	195	—	—

^a All values in kcal mol⁻¹, quoted in Ref. (79MI6).

^b Percent *s* character in lone-pair hybrid, see Ref. (75JA4136).

compound may behave differently. Information concerning the protonation site may be obtained by correlations between the proton affinity data, measured for a family of homologous bases, and the core-electron binding energies (E_B) of their basic site, measured by X-ray photoelectron spectroscopy (77JA4203).

The straight line of unit slope, correlating the N_{1s} binding energies of a variety of nitrogen compounds with their proton affinities, demonstrates that nitrogen is the site of protonation for all of the compounds falling on the line (e.g., pyridine) (Fig. 12). Large deviations from linearity are observed for formamides, whose most favored protonation site must be the oxygen atom. This conclusion is based on a good correlation between the proton affinities of formamides and their O_{1s} binding energies. Pyrrole is another compound that deviates significantly from the correlation. This deviation suggests the carbon atoms of pyrrole as the most favored protonation sites in the gas phase, in agreement with similar conclusions reached in solution by NMR analysis (63JA2763) and on the grounds of theoretical estimates.

If the E_B versus $-\Delta G_B$ correlation analysis is restricted to substituted pyridines (Fig. 13), a considerable scatter from linearity is observed, mostly due to uncertainty in the N_{1s} orbital assignment in aminopyridines

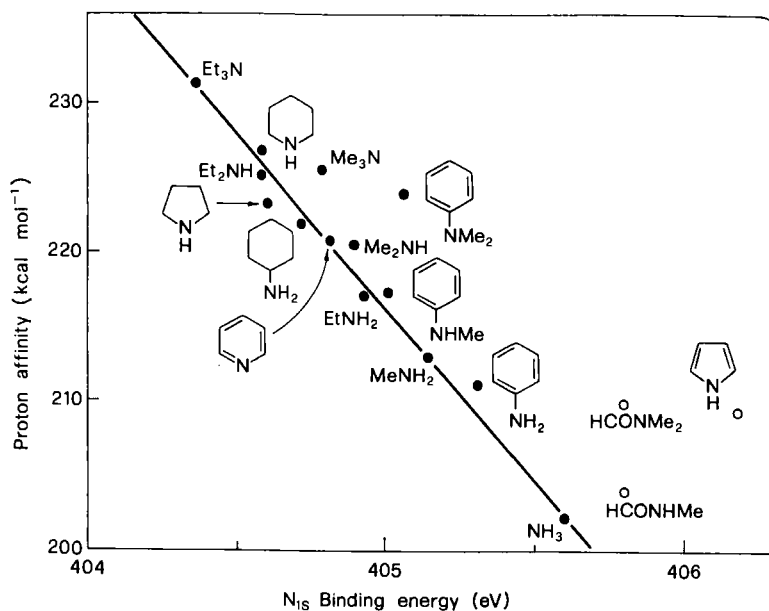


FIG. 12. Correlation of N_{1s} binding energy with proton affinity of various nitrogen compounds (77JA4203).

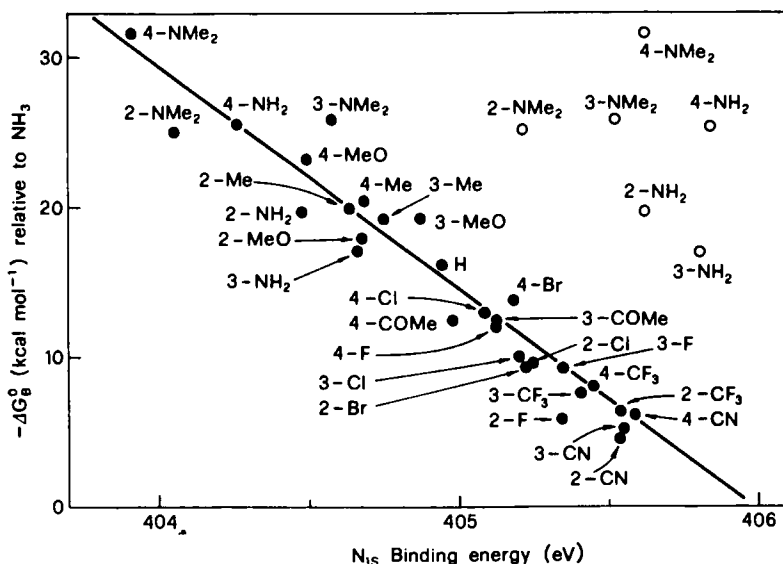
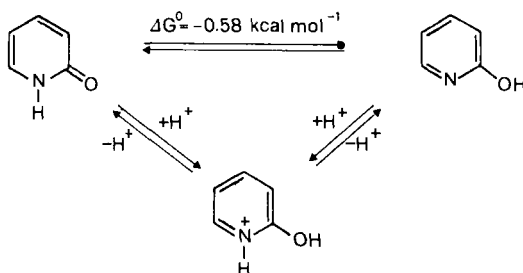


FIG. 13. Correlation of N_{1s} binding energy with gas-phase basicity of substituted pyridines. Open circles represent amino-N ionization (82JA5019).

(82JA5019). In all cases, the value assigned to the ring nitrogen is the one at lowest binding energy and is seen to lie close to the best-fit line. This would clearly indicate that protonation occurs in all cases at the ring nitrogen [83JCS(P2)1735]. On the grounds of similar correlations for substituted nitriles, it is concluded that isomeric cyanopyridines are protonated at their ring nitrogen, in spite of the fact that both ring and nitrile nitrogens have equivalent N_{1s} binding energies.

A special case is that of 2-hydroxypyridine, which is in tautomeric equilibrium with 2-pyridone. At variance with solution equilibrium data (56JCS1294; 58JCS674), application of X-ray photoelectron spectroscopy to the tautomeric 2-pyridone–2-hydroxypyridine pair indicates the latter as the most stable isomer in the gas phase ($\Delta G^0 = -0.58 \text{ kcal mol}^{-1}$; see Scheme 1). From Scheme 1, it is apparent that protonation of tautomeric forms must occur at different sites (N and O, respectively), but leads to the same species. From the cycle, however, the gas-phase basicities of 2-pyridone and 2-hydroxypyridine cannot differ by more than $0.58 \text{ kcal mol}^{-1}$, even though their N_{1s} binding energies differ by some 1.65 eV (76JA6048; 79JA1361). This provides conclusive evidence for the suggestions (74JA5299; 75JA659; 76JA2380; 77JA3980; 79CPL449; 79JA1764; 80JA1174; 80JA5222) that correlations between core-electron binding energies and gas-phase basicities can be valid only if very stringent requirements are satisfied. In particular,



SCHEME 1

good E_B versus PA correlations are normally found for homologous series of compounds when the relaxation energies involved in the removal of a core electron from the basic site are similar for all compounds in the series (74JA5299; 75JA659; 76JA2380; 77JA4203; 79CPL449; 79JA1764). As shown by the 2-pyridone–2-hydroxypyridine tautomers, the correlation breaks down when the sites of protonation and ionization are not the same or when protonation causes substantial geometry changes (76JA2380; 77JA3980; 79JA1764; 80JA1174; 80JA5222). However, a multivariate linear correlation is found to hold for the gas-phase proton affinities of a large family of oxygen, nitrogen, and carbon bases as a function of both their $1s$ binding energies and their first ionization potentials, namely, the two most important factors that contribute to the gas-phase basicity of a given molecule[82JCS(P2)1409]. The weight of these two factors in determining the gas-phase basicity of a molecule can be understood if the protonation process is considered as due to the combination of two distinct steps. The first step is the localization of a positive charge on the basic site by a substantially vertical transition quantitatively measured by the core binding energy of the basic center. This event has a predominant local character, since E_B is rather insensitive to the distribution of the outer valence electrons. The second step is the transfer of electronic charge from the base to the proton, a substantially adiabatic transition related to the polarizability of the entire molecule and adequately measured by the first ionization potential of the molecule. This reasoning seems to be borne out in that there is a good correlation between gas-phase proton affinities and the charge transferred to the proton during the protonation process of azines (Fig. 14) (77JA3617; 77JA5821; 78JA1673).

Excellent linear correlations have been obtained between experimental proton affinities of a number of substituted pyridines and their C_{1s} , O_{1s} , and N_{1s} orbital energies, estimated by *ab initio* calculations (79JA6520). This approach allows prediction of proton affinities for any single position of the substrate as well as of the proton affinity of those compounds, hardly available experimentally [76JA854; 83JCS(P2)1735]. Similar correlations have been found between the n orbital energies, if this orbital is centered on the

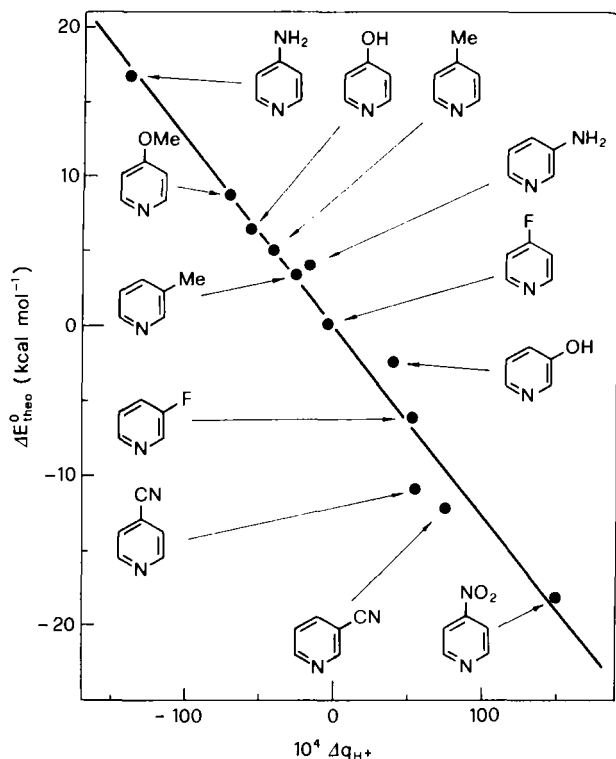


FIG. 14. Correlation of *ab initio* relative proton affinities of substituted pyridines with the corresponding Mulliken charge of the acidic proton of the substituted ion ($XpyH^+$) relative to the unsubstituted one (pyH^+): $\Delta q_H = q(XpyH^+) - q(pyH^+)$ (77JA5821).

ring nitrogen of pyridines, and either experimental PA or the minimum value of the calculated molecular electrostatic potential. These correlations are satisfactory for all pyridines considered, thus confirming their ring nitrogen as the most favored protonation site. Only two exceptions are observed, namely, those involving 4-nitro- and 4-nitrosopyridines, for which protonation may occur at the oxygen atom as well. No direct relationship is obtained between the PAs of substituted pyridines and the net charge at their ring nitrogen atom, thus confirming the relevance of other factors, i.e., the extent of charge transfer from nitrogen to the proton in the protonated intermediate, in determining gas-phase basicities of pyridines.

Analysis of C_α and C_β orbital energies of pyrrole and indole suggests that the preferred protonation site is the C_β atom of both substrates (84JA421), in agreement with predictions based on the corresponding molecular electrostatic potentials (75T915; 78T275). However, the molecular electrostatic potential indicates the most favorable approach of a unit positive charge to

the isolated molecule, although the corresponding attack may not necessarily lead to the most stable substitution intermediate. Similarly, $1s$ binding energy correlations provide information concerning the intrinsic basicity of a given center of the isolated molecule, but quite frequently protonation induces dramatic changes in both the structure and the charge distribution of the substrate. As a consequence, protonation on the kinetically most basic center does not always lead to the most stable protonated form. This appears to be the case for pyrrole, where correlations between site proton affinities and core electron binding energies seem to predict C_β as the preferred protonation sites (77JA4203; 84JA421), whereas the α protonated pyrrole is recognized as the most stable structure on the grounds of semiempirical calculations (Figs. 9 and 11) [59AJC152; 72JCS(P2)479; 77TL3565; 80JPR147]. In the case of indole and its derivatives, instead, protonation on the most basic center, i.e., the C_β atom, leads directly to the most stable protonated form (Table V) (82T3693; 84JA421).

For five-membered heteroaromatic compounds containing two heteroatoms, the preferred protonation sites have been estimated from correlations between their calculated protonation energies (ΔE_p) and several parameters, including the lone-pair orbital energies [83JCS(P2)1869]. A satisfactory linear dependence is observed, which indicates that the preferred protonation site is the heteroatom lone pair. Another useful correlation parameter is the electron density of the proton bound to the basic heteroatom in the cation, q_H [79JCS(P2)1632; 81JA1344], which has been found to apply for substituted pyridines as well (77JA3617; 77JA5821; 78JA1673; 79JA6520). This factor appears to correlate well with the attenuation effect on the basicity when

TABLE V
Ab Initio PROTON AFFINITIES OF SOME INDOLE DERIVATIVES^{a,b}

Compound	Position								
	N-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
Indole	189.6	154.8	210.3	192.0	200.1	192.6	191.5	157.8	196.5
1-Methylindole	188.1	156.8	210.5	192.8	199.3	192.9	192.1	161.4	196.6
2-Methylindole	192.3	151.1	216.6	193.4	201.9	194.4	193.4	160.3	199.2
3-Methylindole	190.0	160.2	204.3	194.6	201.3	193.2	192.2	159.3	200.0
4-Methylindole	190.3	157.2	213.3	185.1	205.4	194.2	194.2	159.6	200.5
5-Methylindole	190.1	155.8	211.2	197.3	192.8	196.1	193.4	159.9	198.7
6-Methylindole	190.1	155.7	211.4	194.5	204.2	185.6	197.0	160.0	198.6
7-Methylindole	190.9	156.3	212.1	194.5	201.6	197.1	184.2	161.7	198.6
2-Aminoindole	196.0	112.7	229.8	200.8	204.3	200.1	195.3	169.1	199.5

^aRef. (82T3693).

^bAll values are in kcal mol⁻¹

passing from the gas phase to solution, owing to the specific interactions with the solvent (e.g., hydrogen bonding) (77MI3). A reasonable correlation is also found with the charge of the basic heteroatom in the neutral five-membered compounds (76MI2; 84JST161), which, however, seems to fail for pyridines (79JA6520). Figure 15 shows the correlation between the calculated protonation energies of a number of substituted pyrazoles and imidazoles as a function of their lone-pair orbital energies [83H1717; 83JCS(P2)1869]. Clearly, significant deviations are observed for the nitro derivatives, which are attributed to some mixing between the orbital located on the ring-nitrogen lone pair and the slightly more energetic one located on the nitro group. This

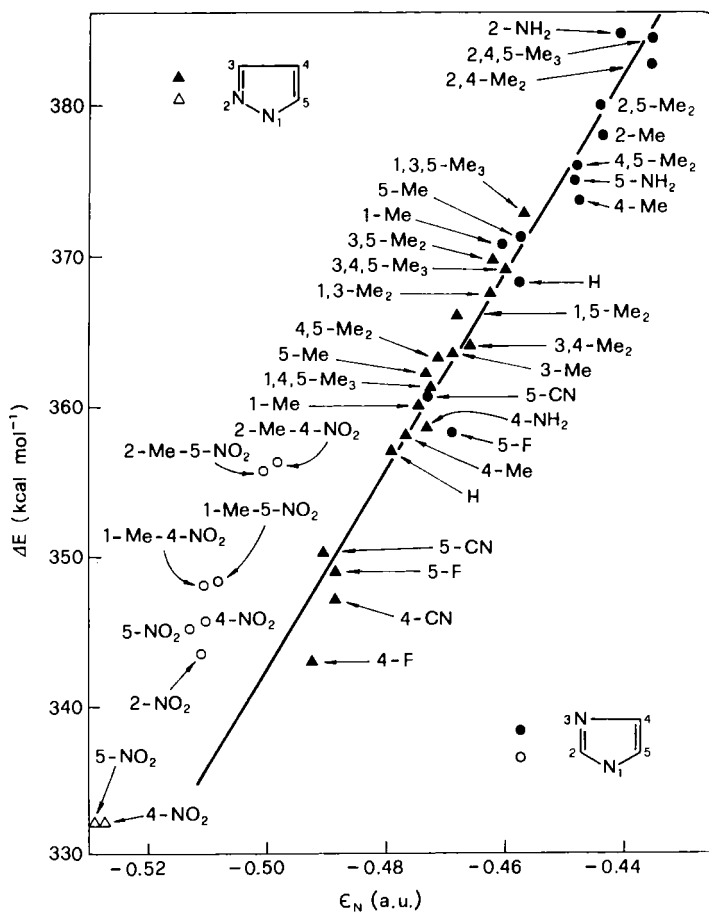


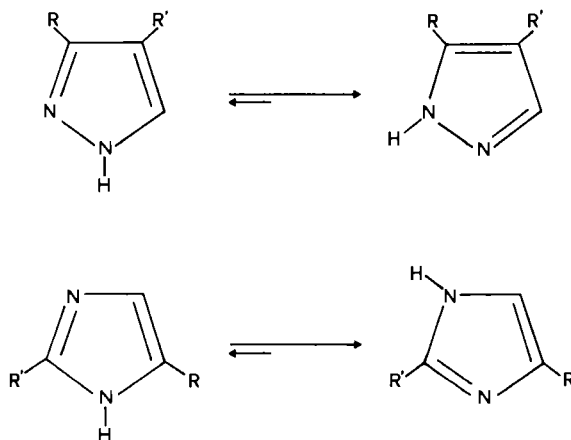
FIG. 15. Correlation of INDO protonation energies (ΔE_p) with lone-pair orbital energies (ϵ_N) of pyrazoles (triangles) and imidazoles (circles) [83H1717; 83JCS(P2)1869].

mixing causes some uncertainty (~ -0.02 au) in the calculated ϵ_N values. Finally, on the grounds of ϵ_N versus PA relationships, it can be expected that gas-phase tautomeric equilibria in the symmetric azoles of Scheme 2 are shifted toward the right side, at variance with solution equilibrium data [83JCS(P2)1869].

Calculated PAs versus *ab initio* C_{1s} and N_{1s} orbital energy correlations have been used to estimate the site of protonation in isomeric indazoles and azaindoles (Table VI) (83JST143; 84JST263; 84NJC87). The most important conclusion is that both indazoles and azaindoles are nitrogen bases. It is also evident that 2-methylindazole is a much stronger base than its tautomer 1-methylindazole. This agrees with observed basicity in solution, where the pK_a value for 2-methylindazole (+2.02) is larger than that for 1-methylindazole (+0.42) (79BSF2619). Indazoles are, however, weaker bases than azaindoles. In particular, 7-methyl-7*H*-pyrrolo[2,3-*b*]pyridine is predicted to be one of the most basic molecules, known at present, in the gas phase. Its estimated proton affinity (PA = 251.5 kcal mole⁻¹) appears consistent with the high basicity shown by this molecule in aqueous solution ($pK_a = 8.9$) (55JA6554).

2. Intrinsic Substituent Effects

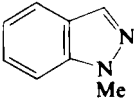
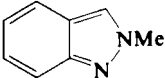
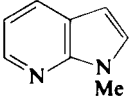
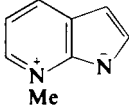
Extensive investigation in the gas-phase, ion-chemistry field allowed observation of a distinct dependence of the reactivity properties of organic compounds on their molecular structure. As far as the thermodynamic



R = Me ; R' = H, Me

SCHEME 2

TABLE VI
Ab Initio PROTON AFFINITIES^a OF ISOMERIC INDAZOLES^b AND AZAINDOLES^c

Compound	Position								
	1	2	3	4	5	6	7	8	9
	174.4	205.7	173.7	175.1	185.9	177.8	177.3	144.3	182.8
	220.3	161.3	156.7	184.8	190.7	192.2	188.7	175.9	190.1
	185.7	150.2	201.4	170.9	187.5	156.8	223.9	127.9	184.0
	251.5	192.7	236.1	150.1	172.2	108.7	167.6	129.3	187.8

^a In kcal mol.⁻¹

^b Ref. (83JST143).

^c Ref. (84NJC87).

properties are concerned, this dependence has been rationalized in terms of a number of intrinsic substituent effects, among which the most important are the polarizability, the inductive field, and the resonance effects (75MI2; 79MI3). Additional kinds of substituent effects, namely, change of hybridization in the substituent group (75JA4136), intramolecular hydrogen bonding (72JA3671; 73JA2699; 73JA3504; 77JA2222; 79MI6), steric effects (75JA4136), and entropy effects (77JA5417; 78JA1953; 79MI7) may play a role as well.

If referred to the properties of the unsubstituted reference compound, the group polarizability effect (*P*) is visualized as arising from the differential in stabilizing charge-induced dipole interaction (68JA6501; 71JA3914; 71JA4608). In the point charge–polarizability approximation this energy is given as:

$$E = -\frac{\alpha q^2}{2\epsilon r^4} \quad \oplus \xleftarrow{r} \left(\xleftarrow{\alpha} \right) \quad (10)$$

+ *q*

where *q* is the charge, α is the polarizability, *r* is the distance of separation, and ϵ is the dielectric constant. The effect of alkyl groups on the basicity of amines, (71JA4314; 72JA4724; 72JA4726; 72JA4728; 73JA3504; 76JA318), phosphines (74JA1604; 80JA2540), and arsines (75IC2887; 77JA5417) and on the acidity of alcohols (74JA4323) can be understood reasonably well in terms of such a model. A highly polarizable substituent (e.g., the alkyl group) will preferentially stabilize the conjugate ion of the organic compound compared to the unsubstituted counterpart. A proton-transfer equilibrium will be shifted by the *P* effect in the direction that places the charge on the most polarizable substituent irrespective of the charge type.

The inductive-field effect (*I*) is visualized as arising from the differential in electrostatic charge–dipole stabilization or destabilization. In the point-charge dipole approximation, this energy is given by

$$E = \frac{q\mu \cos \theta}{\epsilon r^2} \quad \oplus \xleftarrow{\quad} \left(\nearrow_{\theta}^{\mu} \right) \quad (11)$$

+ *q*

where μ is the dipole moment, θ is the orientation angle, and *q*, *r*, and ϵ are as above. Thus, for example, a large dipole moment localized in the substituent group of an acid–base pair will destabilize the ionic species if its orientation places the positive (negative) end of the dipole toward the cationic (anionic) center of the charged species. In these cases, the proton-transfer equilibrium will be shifted by the *I* effect in the direction that favors formation of the neutral substituted compound, if compared to the equilibrium involving the unsubstituted one. Dipole orientation and sign of the ion charge determine the sign of the *I* effect. Inductive-field effects must be interpreted with care because of the possibility of interference from intramolecular hydrogen bonding,

which may provide extra stabilization in the protonated base. Furthermore, in many instances, the intrinsic inductive effect of a substituent may be accompanied by a superimposing polarizability effect of the group, as shown in Table VII, concerning alkyl group effects on the gas-phase basicities and acidities of alcohols. The I values shown in Table VII are in the "classical" inductive order and correlate very well with the empirical-field substituent parameters, σ_I , i.e., $I = \sigma_I \rho_I$, where $\rho_I = -70 \text{ kcal}/\sigma_I$.

For alkyl substituents, the "electron-releasing" inductive effects of the alkyl group relative to CH_3 are substantial, i.e., up to $2.3 \text{ kcal mole}^{-1}$ for *t*-Bu, but nonetheless, these are three to seven times smaller than the corresponding predominant polarizability (P) effects. The values of I are nearly additive in the two series: Me, Et, *i*-Pr, and *t*-Bu; and Et, CH_2CHF_2 , and CH_2CF_3 . However, P values show that saturation occurs in the former series (increments of 3.8, 2.7, and $2.0 \text{ kcal mol}^{-1}$), and in the latter series P is approximately constant.

An *ab initio* theoretical treatment of inductive-field effects has been carried out for β -substituted ethylamines, where hyperconjugative and polarizability effects on proton affinities were minimized and intramolecular

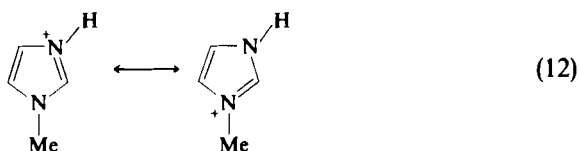
TABLE VII
EVALUATION OF INDUCTIVE (I) AND POLARIZABILITY (P) EFFECT OF
ALKYL GROUPS^a

R	$\delta\Delta G_B^0$	$\delta\Delta G_A^0$	I	P
<i>t</i> -Bu	10.8	6.2	2.3	8.5
<i>i</i> -Pr	8.0	5.1	1.5	6.5
<i>neo</i> -Pent	9.1	7.3	0.9	8.2
<i>i</i> -Bu	8.0	6.1	1.0	7.0
<i>n</i> -Pr	6.5	4.8	0.9	5.6
Et	4.5	3.1	0.7	3.8
Me	(0.0)	(0.0)	(0.0)	(0.0)
$\text{C}_6\text{H}_5\text{CH}_2$	4.8	10.3	-2.8	7.6
$\text{MeO}(\text{CH}_2)_2$	1.0	7.0	-3.0	4.0
F_2CHCH_2	-4.3	13.4	-8.9	4.6
CF_3CH_2	-10.0	16.6	-13.3	3.3

^a I and P effects derived from $\delta\Delta G^0$ values of proton-transfer process: $\text{ROH}_2^+ + \text{MeOH} \rightleftharpoons \text{MeOH}_2^+ + \text{ROH}$ ($\delta\Delta G_B^0 \approx I + P$) and $\text{RO}^- + \text{MeOH} \rightleftharpoons \text{MeO}^- + \text{ROH}$ ($\delta\Delta G_A^0 \approx -I + P$) [R. W. Taft, M. Taagepera, J. L. M. Abboud, J. F. Wolf, D. J. De Frees, W. J. Hehre, J. E. Bartmess, and R. T. McIver, Jr., *J. Am. Chem. Soc.* **100**, 7765 (1978); G. I. Mackay and D. K. Bohme, *J. Am. Chem. Soc.* **100**, 327 (1978)]. The $\delta\Delta G^0$ values are in kcal mol^{-1} ; precision, $\pm 0.2 \text{ kcal mol}^{-1}$.

hydrogen-bonding effects excluded (76JA7438). A satisfactory correlation between $I \simeq \rho_I \sigma_I$ and the calculated equilibrium parameters was observed.

In solution, resonance stabilization (*R*) is commonly the predominant structural driving force of a reaction. Gas-phase proton-transfer equilibria offer a striking contrast, in which the *R* effects are frequently found to be secondary to a predominant combination of *I* and *P* effects. However, it is recognized that for aromatic compounds, such as, for instance, imidazole, resonance stabilization of the protonated form is the predominant contribution determining the relatively high basicity of imidazole and its congeners in the class of five-membered heteroaromatic compounds.



Isolation of *R* from *P* effects provides a greater challenge than does the separation of *I* and *P* effects. This separation also provides uncertain conceptual difficulties, but the solvent effects on certain proton-transfer equilibria appear to provide a tool permitting such a separation.

3. Gas-Phase Basicity of Six-Membered Heteroaromatics

The substantially lower base strength of pyridine ($pK_a = 5.21$) toward the aqueous proton than that of ammonia and aliphatic amines ($pK_a = 9-11$) is generally traced to a greater degree of *s* character in the former's hybrid molecular orbital containing the lone electron pair. In the gas phase, the basicity of pyridine ($PA = 220.4 \text{ kcal mol}^{-1}$) is substantially greater than that of ammonia ($PA = 205.0 \text{ kcal mol}^{-1}$) and comparable with those of aliphatic amines, e.g., Me_2NH ($PA = 220.5 \text{ kcal mol}^{-1}$). This observation clearly establishes that the stability afforded the pyridinium ion by differential polarization of the π molecular orbital between the gas and aqueous phases, as well as other solvation effects (49JCS1293; 58JA1038; 65JA4481), is as large or larger than the hybridization effect. Such a substantial inversion in base strengths of ammonia and pyridine between gas and aqueous phases makes substituent effects on gas-phase proton affinity particularly significant.

A large number of substituted pyridines have been studied in gas-phase proton-transfer equilibria. After correction for polarization effects, the inductive and resonance effects ($I + R$ in Table VIII) of a variety of substituents can be evaluated. Their effects on the relative gas-phase basicities (ΔE°) of pyridines correlate well with the resulting charge density distribution

TABLE VIII
GAS-PHASE BASICITIES, PROTON AFFINITIES, AND DERIVED INDUCTIVE AND RESONANCE EFFECTS FOR
SUBSTITUTED PYRIDINES AT 25°C^a

Pyridine	GB ^b	PA ^c	<i>I</i> + <i>R</i> ^d	Pyridine	GB ^b	PA ^c	<i>I</i> + <i>R</i> ^d
Pyridine	212.6	220.4	—	2-F	204.0	211.8	−8.6
2-Me	215.9	223.7	(3.3) ^e	3-F	207.0	214.8	−5.6
3-Me	215.0	222.8	(2.4) ^e	4-F	209.1	216.9	−3.5
4-Me	215.9	223.7	(3.3) ^e	2-Cl	207.0	214.8	−8.9
2-Et	217.1	224.9	(4.5) ^e	3-Cl	207.9	215.7	−7.1
3-Et	216.1	223.9	(3.5) ^e	4-Cl	210.0	217.8	−5.9
4-Et	216.8	224.6	(4.2) ^e	2-Br	207.8	215.6	−9.3
2- <i>t</i> Bu	218.6	226.4	(6.0)	3-Br	208.5	216.3	−7.6
4- <i>t</i> Bu	218.3	226.1	(5.3) ^e	4-Br	210.1	217.9	−6.7
2,3-Dimethyl	218.4	226.2	(5.8) ^e	2-MeO	213.5	221.3	−3.6
2,4-Dimethyl	219.1	226.9	(6.5) ^e	3-MeO	214.7	222.5	−1.4
2,5-Dimethyl	218.4	226.2	(5.8) ^e	4-MeO	218.8	226.6	+2.0
2,6-Dimethyl	219.3	227.1	(6.7) ^e	2-MeS	214.2	222.0	−4
3,4-Dimethyl	218.4	226.2	(5.8) ^e	4-MeS	217.7	225.5	0
3,5-Dimethyl	217.7	225.5	(5.1) ^e	2-NH ₂	216.0	223.8	+0.1
2,4-Di- <i>t</i> Bu	223.6	231.4	(11.0)	3-NH ₂	213.2	221.0	−1.8
2,6-Di- <i>t</i> Bu	223	231	(11) ^e	4-NH ₂	222	229	+6
4-Vinyl	215.4	223.2	−1.4	2-NMe ₂	221.4	229.2	+4
2-CF ₃	204.0	211.8	−11.9	3-NMe ₂	222.1	229.9	+5
3-CF ₃	205.0	212.8	−10.0	4-NMe ₂	227.9	235.7	+10
4-CF ₃	205.2	213.0	−10.7	2-Cl-4-Me	210.8	218.6	−8.3
2-CN	201.1	208.9	−16.0	2-Cl-6-Me	211	219	−8
3-CN	201.7	209.5	−14.4	2-Cl-6-MeO	208.1	215.9	−12.4
4-CN	202.8	210.6	−14.0	2-CH ₂ OCH ₃	218.2	226.0	(1) ^f
4-CHO	207.4	215.2	−9.4	4-NO ₂	201.7	209.5	−16
4-COCH ₃	209.6	217.4	−8				

^a All values in kcal mol^{−1}.

^b GB values from Refs. (75M12; 76JA854; 77JA5729).

^c Calculated from GB, using symmetry entropy correction (see text).

^d *I* + *R* is the calculated inductive and resonance effect after correction for the polarization effect of the substituent by using a polarization effect for an alkylpyridine of corresponding polarizability.

^e Polarization effect of alkyl group, which may include some inductive effect.

^f The high GB here probably reflects an intramolecularly hydrogen-bonded pyridinium ion.

(Δq_H) in the corresponding pyridinium ions calculated by *ab initio* methods (Fig. 14), thus corroborating the view of a close correspondence between the gas-phase proton affinity of a base and the charge transferred to the proton during its protonation process (77JA5821; 78JA1673). A similar linear relationship has been obtained between the relative proton affinities of 3- and 4-substituted pyridinium ions, which are hydrogen-bonded to a single water

molecule, and Δq_H (77JA5729). Since ΔE° in this case includes substituent-induced changes in hydration energy, this observation suggests that solvation energy depends on the charge density at the site of solvation. This is a significant observation, since it helps rationalize the existence of linear free-energy relationships in solution.

Comparison of the substituent effects on the basicities of substituted pyridines in the gas phase and in solution can be made by plotting the differences in the free energies of ionization in the gas phase [$\delta\Delta G_i(\text{gas})$] versus the corresponding quantities in aqueous solution [$\delta\Delta G_i(\text{aq})$, from the differential $\text{p}K_a$ values]. It is found that the plot of $\delta\Delta G_i(\text{gas})$ versus $\delta\Delta G_i(\text{aq})$ leads to a fairly good linear relationship (Fig. 16) (77JA5729; 79JA1675). However, the slope of the straight line is considerably larger than unity. For substituted pyridines, the slope is about three. This large attenuation of the substituent effect in solution, which is almost equally shared by the *I* and *R* effect (72JA1369), results from the influence of the substituent on the solvation energy, which partially cancels the influence of the substituent on the stability of the isolated pyridinium ions.

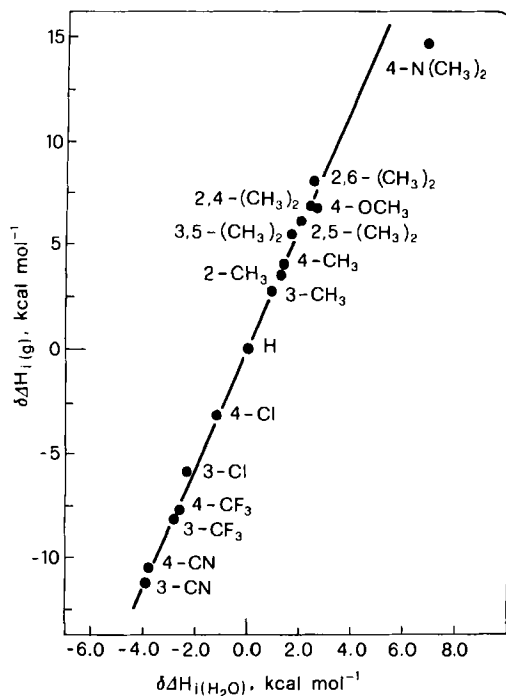


FIG. 16. Correlation of substituent effects on gas-phase proton affinities of pyridines with the corresponding effects on aqueous heats of ionization (77JA5729).

High-pressure mass spectrometric investigation of gas-phase hydration equilibria of substituted pyridinium ions allowed determination of the relevant thermodynamic hydration parameters. A linear relationship between the hydrogen-bonding energies of the pyridinium ion–H₂O pair ($\delta\Delta H$) and the relative basicity of the substituted pyridines (ΔPA) was observed, which is in substantial agreement with previous conclusions (Fig. 17) (79JA1675). Thus the effect of an electron-releasing substituent (e.g., the *p*-NMe₂ group), which increases the relative basicity of an isolated pyridine nucleus, is partially canceled by hydration of the corresponding conjugated acid because of the lower hydration energies (E_s) with respect to those of the unsubstituted ion (Fig. 18).

The picture is qualitatively similar if more than one H₂O molecule is bonded to the pyridinium ions. Each addition of an H₂O molecule contributes to the further stabilization of the cluster, so that differences in the hydration energies of pyridinium ions were no longer observed when the number of H₂O molecules exceeds four. Furthermore, the entropy contribution to the sequential hydration appears to remain small and constant. The change in differential hydration energy of pyridinium ion with the number n of H₂O molecules ($\delta\Delta H_{n-1,n}$) is shown in Fig. 19. Analysis of the curves of Fig. 19

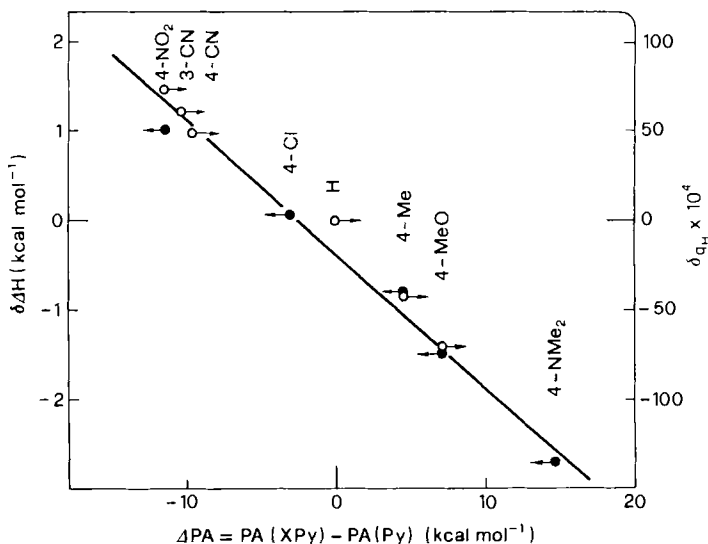


FIG. 17. Correlation of relative basicity (ΔPA) of pyridines with hydrogen-bonding relative energies ($\delta\Delta H$) of the pyridinium ion–H₂O pair. The quantity δq_H shown on the vertical scale on the right gives the net atomic charge difference on the acidic H atom of the pyridinium ion. Open circles, δq_H versus ΔPA ; full circles, $\delta\Delta H$ versus ΔPA (79JA1675).

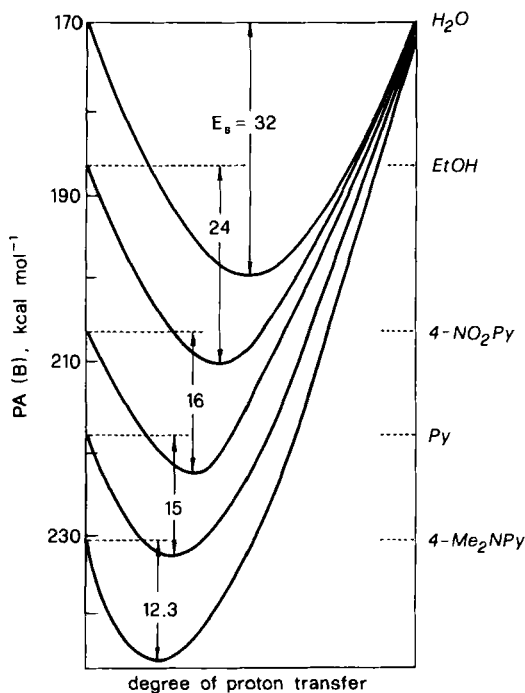


FIG. 18. Plot of stabilization energies E_s due to hydrogen bonding in the pyridinium ion- H_2O pair. The degree of proton transfer from the ion to H_2O (i.e., the horizontal coordinate) is arbitrarily chosen. The curves show that maximum E_s , i.e., maximum hydrogen bonding, is obtained when $\text{PA}(\text{B}) = \text{PA}(\text{H}_2\text{O})$. The greater the PA difference between B and H_2O , the lower the corresponding E_s (79JA1675).

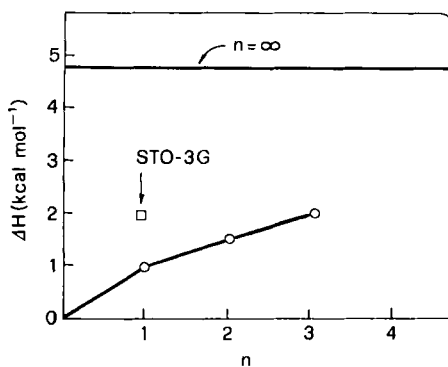


FIG. 19. Enthalpy change for reaction $4\text{-CN-pyH}^+ \cdots (\text{OH}_2)_n + \text{PyH}^+ = 4\text{-CN-pyH}^+ + \text{pyH}^+ \cdots (\text{OH}_2)_n$ versus n . (79JA1675). Results for $n = \infty$ correspond to difference of hydration energies: $\Delta H_{\text{g} \rightarrow \text{H}_2\text{O}}(4\text{-CN-pyH}^+) - \Delta H_{\text{g} \rightarrow \text{H}_2\text{O}}(\text{pyH}^+)$ in liquid water (77JA5729). The square point arises from STO-3G calculations.

indicates that, although the difference of hydration energy of pyridinium ions ΔH tends to increase with n , it is still a long way from the relative hydration energy obtained by Born-type cycles for the same ions ($\delta\Delta H_{g \rightarrow H_2O}$). This observation may be explained on the basis of two effects.

First, the increasing basicity of the $(HOH)_n$ hydrogen-bond framework as n grows may enhance hydrogen-bonding effects on pyridinium ions as the cluster of water molecules hydrogen-bonded to the functional group grows. The second factor involved in the need for a large n can be ascribed to the field effect of the substituted dipole. In liquid water, the field effect of the substituent dipole is attenuated by the high dielectric constant of the aqueous medium. In the small gaseous hydrates of substituted pyridinium ions, the hydrogen-bonded water molecules cluster around the ionic functional group and do not provide a water-molecule network to the substituent. Therefore, little dielectric attenuation of the substituent dipole can occur. Probably, a substantial fraction of the difference between ΔH and $\delta\Delta H_{g \rightarrow H_2O}$ in Fig. 19 is due to the absence of the dielectric attenuation on the gas-phase hydrates.

4. Gas-Phase Basicity of Five-Membered Heteroaromatics

Semiempirical calculations of the site basicities of pyrrole, furan, thiophene, and cyclopentadiene indicate that their α carbons are the most basic positions (81NJC505). These conclusions are in agreement with *ab initio* calculations of the positional basicity of pyrrole (84JA421). The gas-phase proton affinities of pyrrole, for α and β protonation, are estimated to be 208.9 and 205.2 kcal mol⁻¹, respectively, and are in good agreement with the experimental value for pyrrole proton affinity (208.9 kcal mol⁻¹) (79MI6; 82MI3). However, no simple correlation between the proton affinity of pyrrole, furan (196.0 kcal mol⁻¹), and thiophene (195.9 kcal mol⁻¹) (81NJC505) and their molecular properties, core electron or HOMO orbital energies, ionization potential, etc., has been observed. The picture is further complicated if the comparison is extended between the thermodynamic properties (e.g., the proton affinity) of such simple heteroaromatics in the gas phase and the corresponding ones measured, when possible, in solution (e.g., pK_a values). Solution basicity of pyrrole ($pK_a \approx -3.8$) (63JA2763) is many orders of magnitude higher than that of furan ($pK_a \approx -13 \pm 1$) (76T1767), although the gas-phase proton affinity difference is not very large ($\Delta PA = 12.9$ kcal mol⁻¹). The values obtained for indole (202.1 kcal mol⁻¹ for α protonation and 207.1 kcal mol⁻¹ for β protonation) indicate that, in contrast with pyrrole, the β -protonated form is more stable than the α -protonated one. The higher stability of the β -protonated form of indole (207.1 kcal mol⁻¹) with respect to the same form of pyrrole (205.2 kcal mol⁻¹) is accounted for by charge migration from the six- to the five-membered rings (82T3693; 83T2851) and by polarizability effects

[71JA3914; 77JOC3316; 79JA2396; 83AG(E)323] (both absent in pyrrole), which contribute to the extra stabilization of the β -protonated indole. In indole and its methyl derivatives, the most basic site is the β carbon atom, in agreement with the experimental findings in solution. In all cases, the C_α atom is the less basic position (Table V) (82T3693), and protonation at the nitrogen atom cannot compete with protonation at C_β . The basicity of these compounds increases with methyl substitution, with the single exception of 3-methylindole, which presents a PA smaller than that of the parent compound, in agreement with experimental evidence (Fig. 20). All of these results are confirmed by the features of the corresponding molecular electrostatic potentials (Fig. 21) and by the charge distribution calculated for methylated indoles (Table IX). In spite of the greatest electron charge density located at the nitrogen atom of indoles of Table IX, this is not a basic site of the molecules. This is because the nitrogen atom of indoles, as well as that of pyrrole, is a π donor, i.e., it contributes two electrons to the π -electron system, and, in consequence, the lone pair is not available for the proton attachment of the nitrogen atom. The donation of the π charge is accompanied, however, by a stronger withdrawal of σ electrons (σ acceptor), which results in a negative

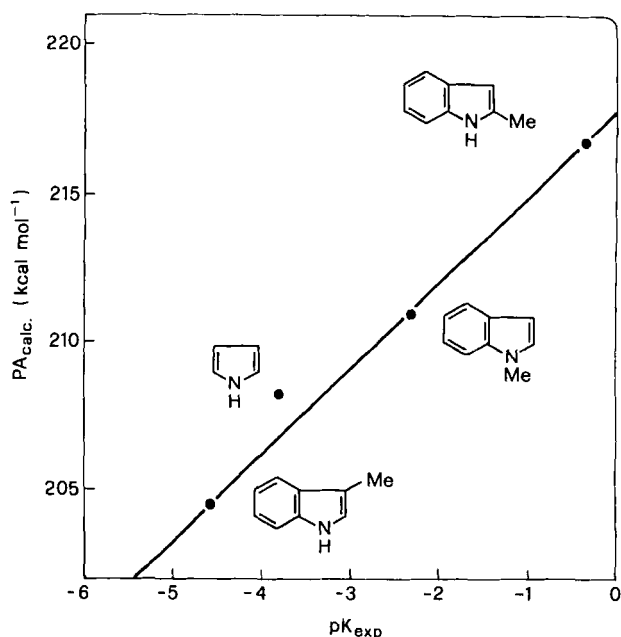


FIG. 20. Correlation between *ab initio* proton affinities and thermodynamic pK_{exp} values of some five-membered nitrogen heteroaromatics (82T3693).

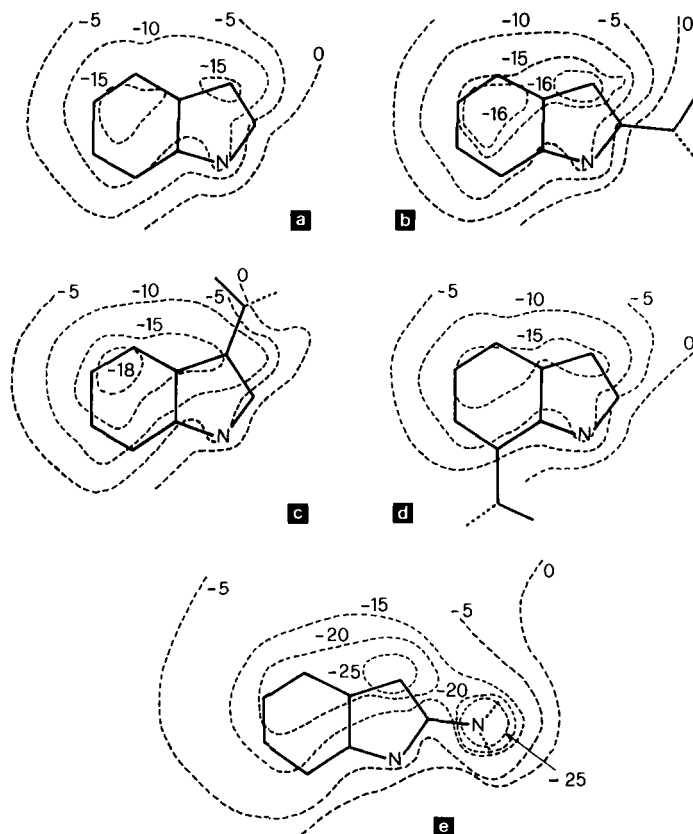


FIG. 21. Electrostatic potential map for (a) indole, (b) 2-methylindole, (c) 3-methylindole, (d) 7-methylindole, (e) 2-aminoindole; each evaluated in a plane 1.6 Å above the molecular plane of the molecule. All values in kcal mol^{-1} (82T3693).

net charge [74JCS(P2)1893; 74ZN(A)624]. As shown in Table IX, the methyl substituents bound to ring carbons always bear a negative charge, indicating that they behave as electron-withdrawing groups by hyperconjugation. The magnitude of such an effect depends on the position of the substituent. When the methyl group is bound instead to the nitrogen atom, it behaves as an electron donor. Similar charge density calculations for azaindole and its two *N*-methyl derivatives indicate that these ring nitrogens, because of their coordination contribution with a lone pair to the aromatic π system, behave as π donors (N-1 in 1 and 2, N-7 in 3), while those that have their lone pair located in a σ -type orbital and contribute with only one electron to the π system behave as π acceptors (N-7 in 1 and 2, N-1 in 3) (Fig. 22).

TABLE IX
Ab-Initio CHARGE DENSITIES FOR INDOLE AND ITS MONOSUBSTITUTED METHYL DERIVATIVES^a

Compound	Position									
	N-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	CH ₃
Indole	-0.575	+0.208	-0.012	+0.060	+0.033	+0.059	+0.018	+0.203	+0.032	
1-Methylindole	-0.526	+0.198	-0.010	+0.062	+0.037	+0.058	+0.023	+0.186	+0.037	+0.116
2-Methylindole	-0.596	+0.231	-0.019	+0.064	+0.036	+0.060	+0.023	+0.210	+0.037	-0.021
3-Methylindole	-0.534	+0.226	-0.035	+0.048	+0.026	+0.048	+0.024	+0.235	+0.014	-0.045
4-Methylindole	-0.583	+0.213	-0.009	+0.084	+0.021	+0.064	+0.021	+0.213	+0.022	-0.059
5-Methylindole	-0.582	+0.215	-0.006	+0.050	+0.057	+0.049	+0.025	+0.208	+0.038	-0.062
6-Methylindole	-0.583	+0.215	-0.006	+0.065	+0.025	+0.080	+0.009	+0.211	+0.035	-0.060
7-Methylindole	-0.585	+0.215	-0.008	+0.062	+0.040	+0.045	+0.044	+0.195	+0.039	-0.053
2-Aminoindole	-0.555	+0.515	-0.137	+0.047	+0.051	+0.058	+0.045	+0.253	+0.054	-0.381 ^b

^a Ref. (82T3693)

^b Charge density of the NH₂ group.

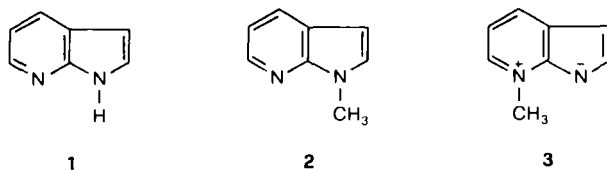


FIG. 22. Kekulé-type structures of 7-azaindole (1), 1-methyl-7-azaindole (2), and 7-methyl-7H-pyrrolo[2,3-*b*]pyridine (3).

Substituted pyrazoles and imidazoles show a linear correlation between their calculated protonation energies ΔE_p at the nitrogen atom and the lone-pair energies ϵ_N of the same atom (Fig. 15) [83H1717; 83JCS(P2)1869]. A similar correlation is found between ΔE_p , calculated on fully optimized geometries, and the total charge of the basic center q_{N_2} . These correlations indicate that a property located on the basic center conveniently describes the modification of the reactivity of that center produced by the polar substituent, thus suggesting that polar effects in these azoles are transmitted via a through-bonds mechanism rather than through-space interactions (81JST263; 82MI4).

The relative gas-phase basicities of imidazole (4), benzimidazole (5), pyrazole (6), indazole (7), 1-methylindazole (8), and 2-methylindazole (9) have been estimated by mass spectrometric methods (Fig. 23) (84OMS627). Although the measurement of $-\log K$ is affected by some uncertainty, the correlation of Fig. 23 suggests that the experimental and the calculated

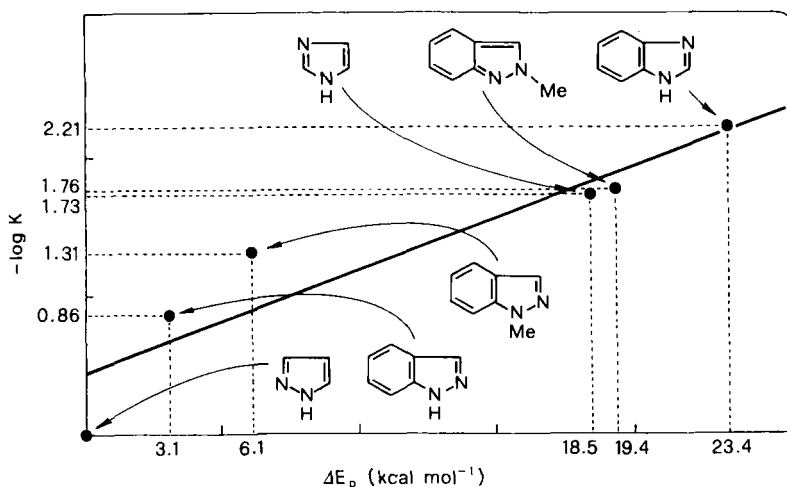


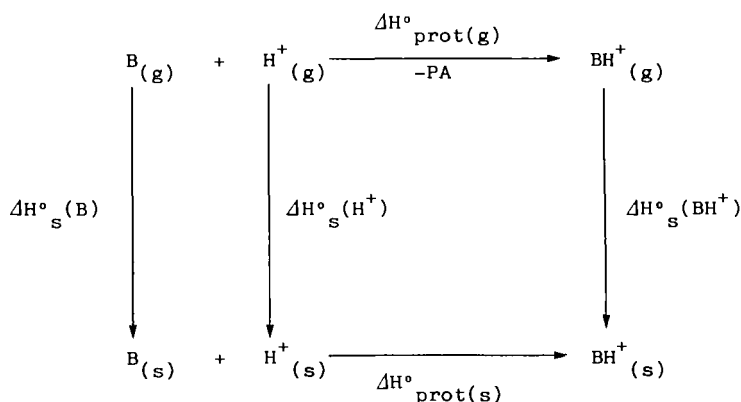
FIG. 23. Experimental gas-phase basicities ($\log K$ values) versus *ab initio* relative protonation energies (ΔE_p) of azoles (84OMS627).

basicity order is the same, namely, $6 < 7 < 8 < 4 < 9 < 5$. The gas-phase basicity order is thus substantially different from that measured in aqueous solution, i.e., 8 ($pK_a = 0.42$) < 7 ($pK_a = 1.31$) < 9 ($pK_a = 2.02$) < 6 ($pK_a = 2.56$) < 5 ($pK_a = 5.77$) < 4 ($pK_a = 7.22$).

A plausible explanation for the inversion of basicity of these heteroaromatics in passing from the gas phase to aqueous solution can be based on the hydrogen bonding between the solvent and both the neutral and the protonated species. In the specific cases of methylindazoles **8** and **9**, their relatively low basicity in aqueous solution may be accounted for by the presence of a methyl group α to the protonation center, which causes charge dispersal and steric hindrance to hydrogen bonding with the solvent [83AG(E)323]. However, the gas-phase basicity difference between **4** (or **6**) and **5** (or **7**) is found to be comparable with experimental values of the effects of benzannellation (≈ -6 kcal mol $^{-1}$) determined for other systems (79JA2396). This indicates that polarizability factors due to the annelated benzene ring may play an important role in the gas phase as well (71JA3914; 77JOC3316). In water, polarizability factors are minimized by dispersion of the positive charge through hydrogen bonding, and therefore benzo derivatives **5** and **7** become less basic than the corresponding parent compounds **4** and **6**. A similar conclusion has been reached in the cases of oxazole and benzoxazole (84JHC269).

C. CORRELATION WITH SOLUTION DATA

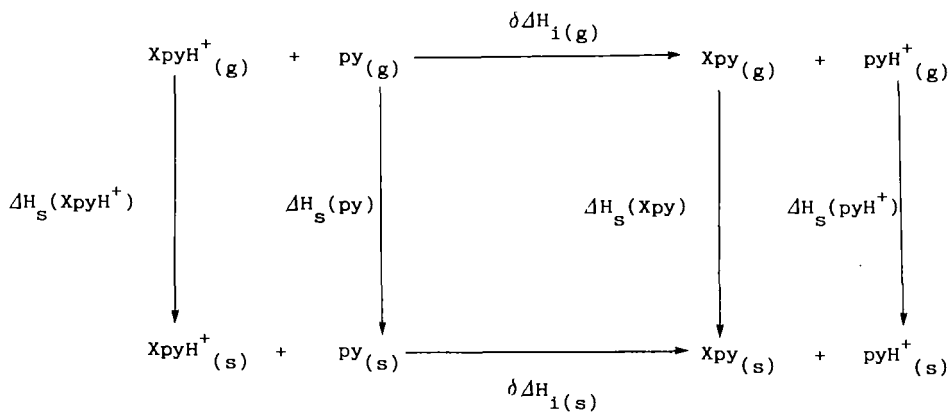
Direct comparison of rates and equilibria in condensed media reveals previously inaccessible facts about ion solvation. As mentioned earlier, comparison of protolytic equilibrium data with relevant gas-phase thermodynamic values demonstrated clearly how powerful is the role that solvation can play in modifying or canceling substituent effects on the basicities of aliphatic amines. Undoubtedly, most of the energy change associated with proton transfer (Scheme 3) in going from the gas phase to solution is due to the charged species of the process and can be traced by classical electrostatics to creating a cavity in the medium and then charging it. Beyond this lies the question of more specific ion-solvent interactions such as hydrogen bonding. The first term is related to the size and the shape of the ion, whereas the second is related to the number and the type of hydrogen-bond interactions between the ion and the basic solvent. Substituted pyridinium ions lend themselves to a discrimination between such factors, since the number of their acidic hydrogens is constant. Furthermore, these species with groups at the γ , β , and α positions cover a considerable range of electron-releasing and -attracting



$$\Delta H^\circ_{\text{prot}}(\text{s}) = -\text{PA} + \Delta H^\circ_{\text{s}}(\text{BH}^+) - \Delta H^\circ_{\text{s}}(\text{B}) - \Delta H^\circ_{\text{s}}(\text{H}^+)$$

SCHEME 3

ability while retaining electrostatic energies of the ions, which are nearly similar in terms of their sizes and shapes. In the case of substituted pyridines, Scheme 3 becomes Scheme 4, where $\delta\Delta H_i(\text{g})$ is the gas-phase basicity change for the isodesmic (70JA4796) proton transfer from the substituted pyridinium ion (XpyH^+) to pyridine (py). The corresponding value in aqueous solution is $\delta\Delta H_i(\text{s})$. The heat of solution of pyridine (py) or substituted pyridine (Xpy) into water from the gas phase is $\Delta H_{\text{s}}(\text{py})$ or $(\Delta H_{\text{s}}(\text{Xpy}))$. Accordingly, the relative value is defined as $\delta\Delta H_{\text{s}}(\text{B}) = \Delta H_{\text{s}}(\text{Xpy}) - \Delta H_{\text{s}}(\text{py})$. Finally, the



SCHEME 4

hydration enthalpy for $XpyH^+$ relative to pyridinium ion is defined as $\delta\Delta H_s(BH^+) = \Delta H_s(XpyH^+) - \Delta H_s(pyH^+)$.

As seen in Scheme 4, the entire difference between $\delta\Delta H_i(g)$ and $\delta\Delta H_i(s)$ for a given pyridine base must ipso facto be due to the difference between the relative solution enthalpies of the neutral base [$\delta\Delta H_s(B)$] and its pyridinium ion [$\delta\Delta H_s(BH^+)$]. Estimates of such differences are reported in Table X.

Analysis of these thermodynamic data indicates that the equilibria shown in Scheme 4 may be understood on a quantitative basis, as can the aqueous solvent attenuation factor of 2.5 seen in Fig. 16, in terms of chemical hydrogen-bonding interactions of bulk water with the pyridinium ions and with the pyridines. *Ab initio* estimates (77JA5729), supported by high-pressure mass spectrometric data (79JA1675), give a single water molecule's attenuation factor of 1.4 for the energy changes for proton transfer between substituted pyridines. By comparison, the aqueous solvent attenuation factor of 2.5 can be explained if one considers that bulk liquid water has about twice as strong a hydrogen-bond acceptor effect as monomeric water toward

TABLE X
SUBSTITUENT EFFECTS IN PYRIDINES ON GAS-PHASE AND AQUEOUS-SOLUTION BASICITIES AND IONIZATION HEATS AND ON HEATS OF TRANSFER FROM THE GAS PHASE TO AQUEOUS SOLUTION FOR PYRIDINES AND PYRIDINIUM IONS^{a,b}

Pyridine substituent	$\delta\Delta G_i(s)$	$\delta\Delta H_i(s)$	$\delta\Delta G_i(g)$ $\cong \delta\Delta H_i(g)^c$	$\delta\Delta H_s(B)$	$\delta\Delta H_s(BH^+)$
4-N(CH ₃) ₂	5.94	6.93	14.6	—	—
2,6-(CH ₃) ₂	2.18	2.44	8	-2.88	2.7
2,4-(CH ₃) ₂	2.01	2.37	6.9	-2.58	1.9
4-OCH ₃	1.87	2.55	6.7	-2.20	2.0
2,5-(CH ₃) ₂	1.43	2.02	6.1	-2.61	1.5
3,5-(CH ₃) ₂	1.13	1.59	5.5	-2.53	1.4
4-CH ₃	1.12	1.30	4.0	-1.34	1.4
2-CH ₃	1.09	1.40	3.5	-1.24	0.9
3-CH ₃	0.63	0.91	2.7	-1.12	0.7
H	(0.00)	(0.00)	(0.0)	(0.00)	(0.00)
4-Cl	-1.88	-1.22	-3.1	—	—
3-Cl	-3.28	-2.44	-5.8	-1.1	-4.5
3-CF ₃	-3.75	-2.8 ^d	-8.1	—	—
4-CF ₃	-3.52	-2.58	-7.8	0.27	-4.9
4-CN	-4.57	-3.75	-10.5	1.90	-4.8
3-CN	-5.27	-3.92	-11.3	—	—

^aAll values in kcal mol⁻¹

^bRef. (77JA5729).

^cRefs. (76JA854; 77JA5417).

^dEstimated.

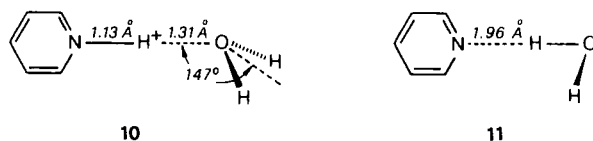


FIG. 24. Partially optimized geometries for hydrogen-bonded complexes between pyridinium ion (10) or pyridine (11) and water (77JA5729).

pyridinium ions and twice as strong a hydrogen-bond donor effect toward the pyridines (Fig. 24). There is close agreement between experimental data and theoretical calculations, showing that the magnitude of the substituent effects on hydrogen bonding to the pyridinium ions is about four times greater in magnitude (but opposite in sign) than that for hydrogen bonding to the pyridines. Heats of transfer of the pyridinium ions and of the pyridines from the gas phase to dilute aqueous solution are found to be somewhat complicated composites of hydrogen bonding, cavity, van der Waals interactions, and water structure modification terms (73MI4). However, substituent effects on contributions of the latter three terms are nearly additive and thus cancel in the difference between the corresponding heat of the transfer of the ion and the neutral pyridine. This particularly fortunate situation arises from the optimal choice of the pyridine series for checking the hydrogen-bond solvation model. Such a series offers ions and molecules of very similar sizes and shapes with substituents distant enough to maintain nearly constant cavity formation and structure-modifying terms, as well as allowing for the cancelation between pyridinium ion and corresponding pyridine of van der Waals dispersion force terms. In accord with these conditions, the substituent effects on entropies of ionization in water are relatively small ($\sim \pm 3$ eu) in this series. No similar relationships are expected for structural effects on gas-phase and solution proton-transfer equilibria involving organic bases that do not satisfy the above conditions (75MI2; 79MI3). Even within the very restricted pyridine series, the approximately linear relationship observed is indeed a very special case because of the very limited structural variation permitted. Indeed, deviations from this relationship from many 2- and 2,6-substituted pyridines have been observed (Fig. 25) (76JA854; 78JPC1268). These can be mainly attributed to the hydrophobic effect of the groups adjacent to nitrogen in both the pyridinium ion and the free base, which restricts access and thus hydrogen bonding to the nitrogen atom or to a proton attached to it ($\delta\Delta G$ values shown in Table XI) [79JA7141; 83JCS(P2)45]. Steric hindrance has been found to be responsible for dramatic deviations from the nucleophilic order (N) of 2-substituted pyridines in solution as well (Fig. 26) (81JOC635).

As mentioned earlier, the thermodynamic properties of unsubstituted five-membered heteroaromatics with one heteroatom do not correlate with the

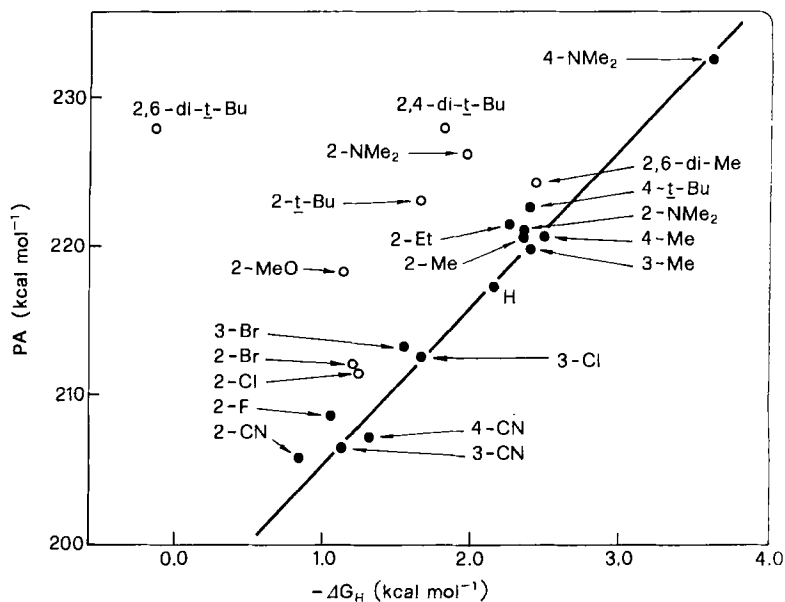


FIG. 25. Plot of proton affinities of substituted pyridines (PA) versus their hydrogen-bonding Gibbs free-energy change ($-\Delta G_H$) for the pyridine + phenol \rightleftharpoons complex reaction (76JA854; 78JPC1268).

TABLE XI
THERMODYNAMIC PROPERTIES FOR IONIZATION AND HYDRATION OF PYRIDINES AND THEIR CONJUGATE ACIDS^a

Substituted pyridines	$\delta\Delta H_s(B)^b$	$\delta\Delta H_s(BH^+)^b$	$\delta(T\Delta S_s)(B)^b$	$\delta(T\Delta S_s)(BH^+)^b$	$\delta\Delta G_s(B)$	$\delta\Delta G_s(BH^+)$
2,6-di- <i>t</i> Bu	-1.7	6.7	-5.99	-8.3	4.29	15.0
4- <i>t</i> Bu	-1.9	1.3	-2.13	-3.17	0.23	4.47
2,6-(CH ₃) ₂	-2.88	2.7	-2.98	-3.22	0.09	5.91
2,4-(CH ₃) ₂	-2.58	1.9	-2.41	-2.88	-0.17	4.72
2,5-(CH ₃) ₂	-2.61	1.5	-2.59	-3.15	-0.02	4.65
3,5-(CH ₃) ₂	-2.53	1.4	-2.39	-2.83	-0.15	4.24
4-CH ₃	-1.34	1.4	-1.10	-1.24	-0.24	2.64
2-CH ₃	-1.24	0.9	-1.31	-1.58	0.08	2.49
3-CH ₃	-1.12	0.7	-1.04	-1.29	-0.08	1.99
H	(0.00)	(0.0)	(0.00)	(0.00)	(0.00)	(0.00)
3-Cl	0.88	-2.48	-0.21	-0.63	0.67	-1.85
2-Cl	0.11	-1.41	-0.18	-1.10	0.29	0.31

^aRef. (79JA7141). All values in kcal mol⁻¹ relative to pyridine.

^bRef. (77JA5729).

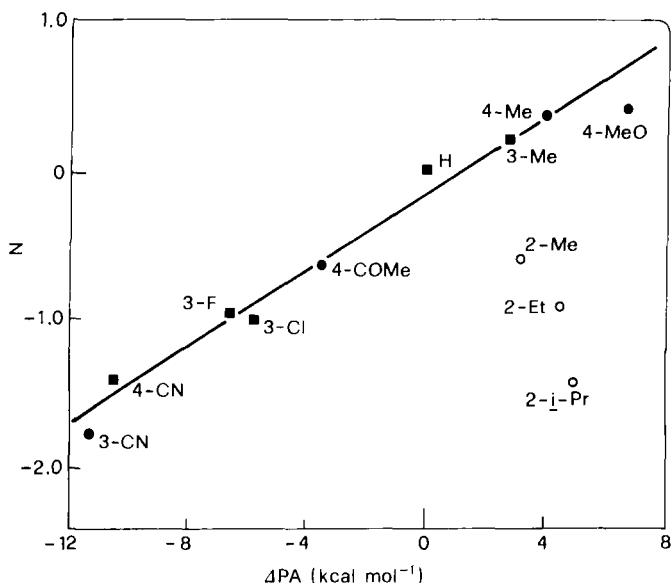
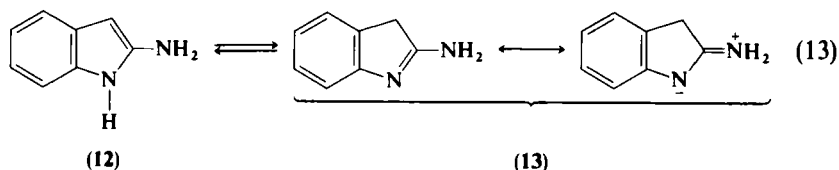


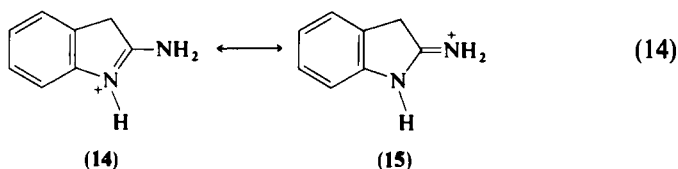
FIG. 26. Correlation of relative proton affinities of pyridines (ΔPA) with their solution nucleophilicities (N) toward methyl fluorosulfonate in 2-nitropropane at 25°C (squares) and ethyl iodide in nitrobenzene at 60°C (circles) (81JOC635).

behavior of the same substrates in solution. Among the nitrogen heterocycles, pyrrole, indole, and their methylated homologs are strong bases in the gas phase, although they exhibit quite low basicity in aqueous solution. A satisfactory linear correlation between thermodynamic pK_a values (62JA2534) of these substrates and their calculated PAs (82T3693) is nevertheless observed (Fig. 20). This correlation arises because the protonation site for all members of the family is a carbon atom, and, therefore, the interaction between the protonated species and the solvent must be quite similar for all of them. In addition, the protonated species is characterized by extensive charge dispersal throughout the molecule. It follows that carbon-protonated species of this type are poorly solvated in solution on account of the absence of exposed atomic sites with appreciable localized positive charge. This explains why a high concentration of hydrogen ions is required to protonate pyrrole and indoles and why the base strength in the gas phase is higher than that in solution.

While pyrrole, indole, and their methyl derivatives behave as weak bases in solution, 2-aminoindole (**12**) presents a considerable pK_a value (8.5) (72MI2), which has been explained by assuming that the molecule exists preferentially as the 2-aminoindolenine tautomer (**13**) [Eq. (13)].



However, protonation of 2-aminoindole at C_β leads to a noticeable contribution of the two mesomeric forms **14** and **15** [Eq. (14)], one of which localizes the positive charge on the NH_2 group. Contrary to the situation prevailing in methylindoles, this favors a strong interaction with the solvent and therefore increases the basicity of **12** in solution. It is concluded that the high $\text{p}K_a$ of **12** does not necessarily indicate that this molecule exists essentially in its tautomeric form **13** in solution.



Comparison of the $\text{p}K_a$ values of a variety of pyrazoles and imidazoles versus the ϵ_N energies (and, presumably, the proton affinities) shows the existence of three families of compounds (Fig. 27) [83JCS(P2)1869]. Each family is characterized by having two (line C), one (line B), or no (line A) methyl groups in the position α to the basic center (the N lone pair). Both steric hindrance to solvation of the cation and charge dispersion (75MI2; 79MI3) through hydrogen bonding with solvent could explain why the α -methyl derivatives have in aqueous solution basicities lower than calculated (about 1.8 $\text{p}K_a$ units, the vertical separation of the lines in Fig. 27). If the solvent effect could be removed, the points of Fig. 27 belonging to compounds with α -methyl groups would be shifted vertically toward the upper line A. This effect is about the same for both families of pyrazoles and imidazoles, but considerably greater than that observed in other nitrogen-containing cyclic bases, e.g., pyridines (81JOC891). As evident from the correlations of Fig. 28, there is a clear difference between the substituent effects on the gas phase and on the aqueous solution basicities of methylated pyrazoles (Fig. 28a) and imidazole (Fig. 28b) (84JOC4379). In fact, in the gas phase, methylation always causes an increment of the corresponding basicity, almost regardless of the position that undergoes substitution. In aqueous solution, however, this is not true for *N*-methyl-substituted compounds (line A), whose basicity in solution is always smaller than that of the corresponding *C*-methylated isomers having similar gas-phase basicity (line B). This attenuation of the solution basicity upon *N*-methylation, which on the average is about 1.0 kcal mol^{-1} (0.7 $\text{p}K_a$ unit) for

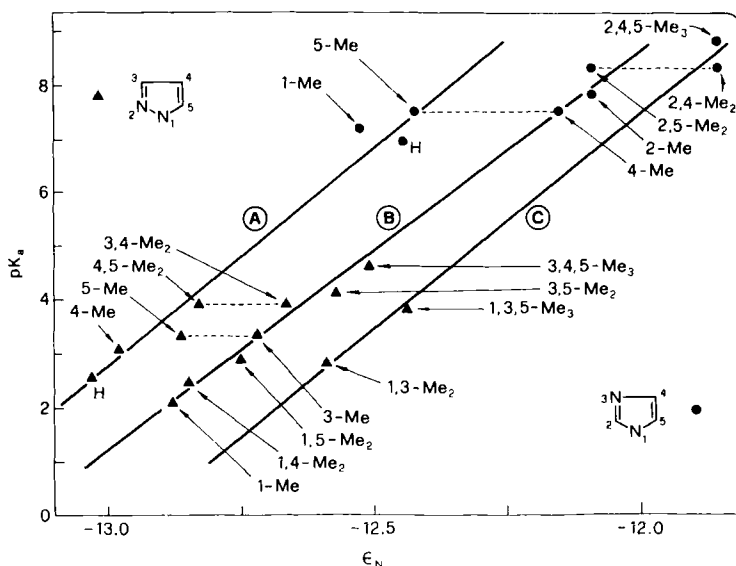


FIG. 27. Correlations of pK_a values versus INDO lone-pair energies (ϵ_N in eV) of pyrazoles (triangles) and imidazoles (circles) with zero (line A), one (line B), or two methyl groups (line C) in a position α to the basic nitrogen [83JCS(P2)1869].

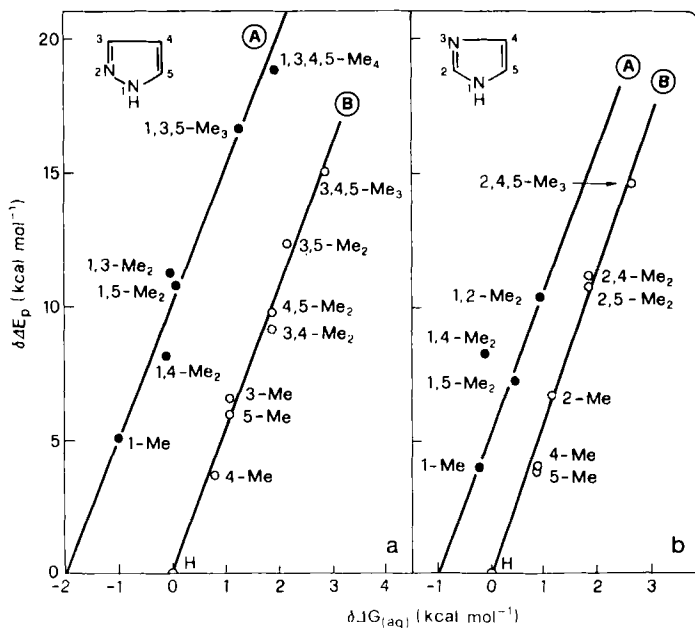


FIG. 28. Gas-phase *ab initio* protonation energies ($\delta\Delta E_p$) versus aqueous solution protonation energies ($\delta\Delta G_{aq}$): (a) methylpyrazoles, (b) methylimidazoles. Lines A, *N*-methyl-substituted azoles; lines B, *C*-methyl-substituted azoles. All values relative to the corresponding unsubstituted parent compounds (84JOC4379).

imidazoles, amounts to ~ 2.0 kcal mol $^{-1}$ (1.4 pK $_a$ units) for pyrazoles. This quantitative difference is explained by noting that the methyl group in *N*-methylpyrazoles, besides preventing solvation of one active center (the N-1 atom) if compared to the unsubstituted parent compound, causes some steric hindrance to solvation of the adjacent protonic center (the N-2 atom). The latter effect is obviously much less important for *N*-methylimidazoles. Attenuation of solution basicity on N-methylation is not constant but follows an inverse correlation with the intrinsic basicity, reflecting a parallel weakening of the hydrogen bond between the protonated molecule and the solvent.

Solvent effects are found to operate in a similar way with regard to the basicity of azoles, benzazoles, and benzazoles carrying a methyl group α to the basic center (84JHC269). Again, three families of compounds, whose pK $_a$ values correlate with the ionization energy of the nitrogen lone pair (the basic

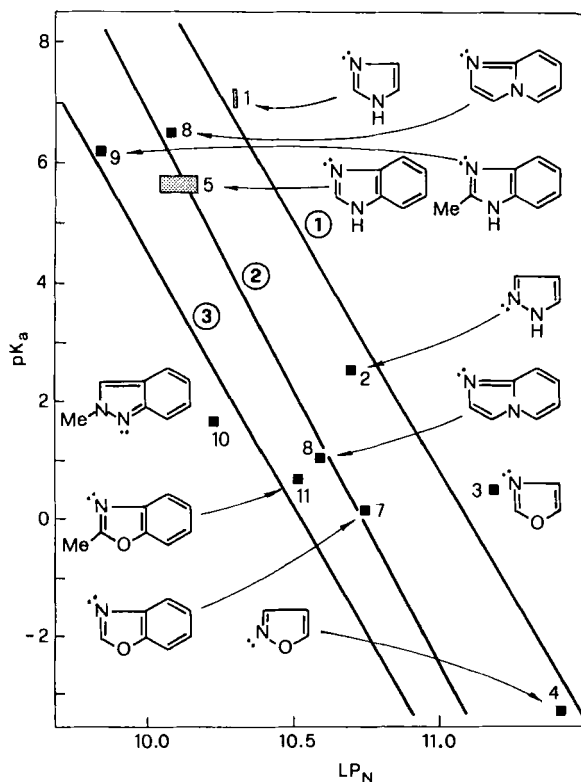


FIG. 29. Correlations of pK $_a$ values versus nitrogen lone-pair vertical ionization energies (LP $_N$ in eV) of simple unsubstituted azoles (line 1), unsubstituted benzazoles (line 2), and 2-methyl-substituted benzazoles (line 3) (84JHC269).

center), are recognized (Fig. 29). The same relationships include azoles containing two nitrogen atoms (e.g., imidazole, pyrazole) or a nitrogen atom and an oxygen atom (e.g., oxazole, isoxazole), thus suggesting that specific solvent effects on the basic site are the major factors that determine the basicity difference between gas phase and solution. Furthermore, as observed for indoles (73MI6) and benzimidazole [83AG(E)323], benzannulation decreases the aqueous basicity (by about 2.8 pK_a units). Finally, the presence of a methyl group α to the basic nitrogen further decreases the basicity (by about 2.0 pK_a units).

V. Kinetics and Mechanisms

A. GAS-PHASE REACTIVITY

Laboratory kinetic measurements of reactivity have indicated that most of the exothermic bimolecular ion-molecule reactions in the gas phase proceed extremely rapidly at thermal energies, i.e., with k values ranging between 10^{-10} and 10^{-8} $\text{cm}^3 \text{ molecule}^{-1} \text{ sec}^{-1}$. It can be inferred from these experimental findings that many gas-phase ion-molecule reactions, if energetically allowed, often proceed on nearly every collision, i.e., that the reaction-rate coefficient is nearly equal to the collision rate of the ion with the molecule. This is a consequence of long-range attractive forces between the ion and the neutral, which lead to an encounter complex characterized by an energy minimum on the potential surface. The encounter complex is excited by the electrostatic energy ϵ_0 released in the association process (Fig. 30). Therefore, it may be able

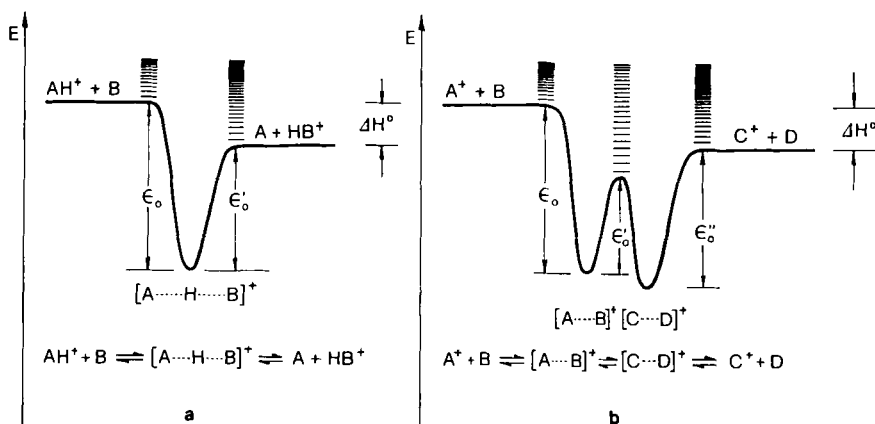


FIG. 30. Potential surfaces (energy versus reaction coordinate) for typical gas-phase, ion-molecule reactions: (a) proton-transfer reactions, (b) electrophilic displacement reactions.

to dissociate to the products unimolecularly (Fig. 30a) or, alternatively, rearrange to another ionic intermediate before dissociating to the products (Fig. 30b).

It is therefore evident that a detailed analysis of the gas-phase reactivity properties of an ion toward a neutral substrate, and of the mechanism leading to the reaction products, requires information regarding the capture cross section of the ion by the neutral and the shape of the ensuing energy profile.

For a system having a Maxwell-Boltzmann energy distribution, current classical theories of ion-molecule interactions predict a collision or capture rate coefficient given by

$$k_c = 2\pi e \left(\frac{\alpha}{\mu} \right)^{1/2} + C \left(\frac{2\pi e \mu_D}{\mu} \right) \left(\frac{2\mu}{\pi k T} \right)^{1/2} \quad (15)$$

$\longleftarrow A \longrightarrow \quad \longleftarrow B \longrightarrow$

where e is the charge on the ion, μ the reduced mass of the collidants, α the polarizability, and μ_D the permanent dipole moment of the neutral molecule (79MI8). This equation is composed of the pure polarization Langevin term A (58JCP294) and a "correction" term B , reflecting the ion-permanent dipole interaction. In the Average Dipole Orientation (ADO) theory, C is a measure of the extent to which the dipole is oriented with respect to the direction of the approaching ion (73IJM347). For $C = 1$, the equation is reduced to the "locked-dipole" limit (63JCP1431; 67CJC3107). The major assumption in the original formulation of ADO theory is that there is no net angular-momentum transfer between the rotating molecule and the ion-molecule orbital motion. While this assumption is adequate at large ion-molecule separation, it tends to become invalid as the separation decreases toward the capture limit. The approximate inclusion of conservation of angular momentum into the ADO theory is the essence of the ADO theory with Conservation of the Angular Momentum (the AADO theory) (78JCP2243).

Ion-molecule rate constants, predicted by these theories, show a satisfactory agreement with the experimental ones, as illustrated in Table XII for a set of proton-transfer processes. Furthermore, the data in Table XII confirm the view that rate coefficients for reactions between a given ionic species and homologous substrates are expected to fall within the same order of magnitude. Similar rate-constant coefficients for reactions involving a given ionic species and molecules with comparable polarizability and dipole momentum can therefore be expected.

Displacement reactions, such as those conceivably involved in hetero-aromatic substitutions, are not well correlated with the overall exothermicity of the process and are found to depend in detail on the specific ionic species, the electronic properties of the substrate, and the nature of the leaving group. In other words, the kinetic parameters and the reaction mechanism of these

TABLE XII
EXPERIMENTAL AND THEORETICAL RATE CONSTANTS FOR SOME ION-MOLECULE REACTIONS^a

XH^+ or X^-	k_{exp}	k_{ADO}	k_{AAADO}	$k_{\text{exp}}/k_{\text{ADO}}$	$k_{\text{exp}}/k_{\text{AAADO}}$
Reaction Type: $\text{XH}^+ + \text{NH}_3 \rightarrow \text{NH}_4^+ + \text{X}$					
H_3^+	4.2	3.98	4.52	1.06	0.93
NH_3^+	2.5	2.18	2.48	1.15	1.01
CH_3^+	2.5	2.18	2.48	1.15	1.01
H_3O^+	2.4	2.12	2.41	1.13	1.00
HCO^+	2.4	1.94	2.21	1.24	1.09
N_2H^+	2.3	1.94	2.21	1.19	1.04
C_2H_3^+	2.1	1.94	2.21	1.08	0.95
C_2H^+	2.0	1.92	2.18	1.04	0.92
N_2OH^+	2.1	1.81	2.05	1.16	1.04
C_4H_8^+	1.9	1.75	1.99	1.09	0.95
C_3H_7^+	1.9	1.82	2.07	1.04	0.92
Reaction Type: $\text{XH}^+ + \text{HCN} \rightarrow \text{H}_2\text{CN}^+ + \text{X}$					
H_3^+	7.4	6.48	7.50	1.14	0.94
H_3O^+	3.5	3.20	3.88	1.09	0.90
N_2H^+	3.2	2.86	3.47	1.12	0.92
HCO^+	3.0	2.86	3.47	1.05	0.86
Reaction Type: $\text{X}^- + \text{HCN} \rightarrow \text{CN}^- + \text{XH}$					
H^-	15	10.8	13.11	1.39	1.09
D^-	9.9	7.8	9.45	1.27	1.05
NH_2^-	4.8	3.37	4.08	1.42	1.18
OH^-	4.1	3.31	4.00	1.24	1.03
C_2H^-	3.9	2.97	3.60	1.31	1.08
SH^-	2.9	2.77	3.34	1.05	0.87
Reaction Type: $\text{XH}^+ + \text{CH}_3\text{CN} \rightarrow \text{CH}_3\text{CNH}^+ + \text{X}$					
H_3^+	10	8.40	10.64	1.19	0.94
H_3O^+	4.7	3.91	5.36	1.20	0.88
N_2H^+	4.1	3.42	4.69	1.20	0.87
HCO^+	4.1	3.42	4.69	1.20	0.87
N_2OH^+	3.8	3.05	4.18	1.25	0.99
CO_2H^+	4.1	3.05	4.18	1.34	0.98

^aAll rate constants $\times 10^9 \text{ cm}^3 \text{ molecule sec}^{-1}$ (79MI8).

reactions appear to be heavily determined by their energy profile, i.e., by the intimate interaction established within the transition state.

The general model for an ion-molecule substitution process in the gas phase involves formation of a reactant encounter complex (AB^+), conversion over an energy barrier ϵ'_0 to a product encounter complex (CD^+), and dissociation to products (Fig. 30b).



First, we should recognize that it is convenient to speak of a reaction efficiency that represents the fraction of encounters that result in product formation. This eliminates the differences in encounter rates that are "physical" [Eq. (15)] rather than chemical in origin. The efficiency of the reaction depends on the relative values of k_{-1} , k_p , k_{-p} , and k_{-2} . Under the collisionless conditions of low-pressure, ion-molecule reactions (e.g., under ICR conditions), the complexes AB^+ and CD^+ are chemically activated. In fact, they contain the thermal and kinetic energy initially associated with the reactants and the electrostatic energy ϵ_0 liberated in their association process. Thus the rate constants, k_{-1} , k_p , etc., are not thermally averaged rate constants but rather microscopic rate constants averaged over an appropriate energy distribution function. The potential surface appears as shown in Fig. 30b. Different reaction efficiencies, often observed for ionic processes of this type, appear, at first glance, unexpected, since there is clearly always enough energy to cross the barrier associated with k_p , while there is only just enough energy to cross back via k_{-1} . The answer lies in what the kineticist recognizes as a very large difference in entropies of activation or preexponential A factors. The forward reaction k_p is, in effect, a unimolecular isomerization with a comparatively "tight" transition state (low A factor). The back dissociation k_{-1} is a fragmentation reaction with an exceptionally "loose" transition state involving essentially free rotations of the product fragments (high A factor). Thus although energy favors k_p , entropy favors k_{-1} . The efficiency of the reaction thus results from a trade-off between these two effects. In more formal terms, it is the available sum of states, weighted by the appropriate energy distribution function, that determines the branching ratio between k_{-1} and k_p . The density of states is determined both by the energy above the critical energy (E) and also the frequencies of the oscillators that affect the A factor. It is easy to see how this model can be extended to more complex situations in which there is more than one product channel. Since in general the transition state for the particular reaction will reflect factors in addition to the overall exothermicity, one should not expect that the product branching ratios will follow the exothermicities of the competing processes leading to the products.

There are some interesting consequences of this model, which can be experimentally tested. For instance, it predicts that slow reactions should become slower with increasing energy (negative temperature dependence). Eventually, of course, alternative reaction paths will become accessible and the reaction rate may increase. It is clearly predicted that complex polyatomic species will react more slowly than simpler species with the same barrier height because of losses in ΔS_{rot} . At higher pressures (e.g., in the ion source of a high-pressure mass spectrometer or in radiolytic and decay systems), back dissociation of the intermediate complexes is prevented by multiple deactivating collisions with an unreactive third body. In the same way, the efficiency of

some high-energy reaction channel may be heavily depressed by the internal-energy loss of the intermediate species by unreactive collisions. The net effect of collisional deactivation is therefore complex, especially in the intermediate pressure range. At sufficiently high pressures (infinite-pressure limit), the reactants pair is fully equilibrated with the bath gas, and the reaction proceeds by purely thermal activation. Under these conditions, substitution reaction paths may be favored by the action of a reactive third body on the collision complex in complete analogy with similar processes in solution.

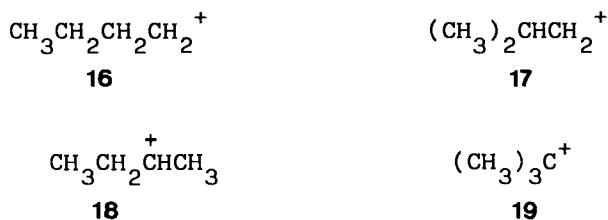
B. REACTION MECHANISM AND ORIENTATION

Interest in the gas-phase reactivity properties of heteroaromatic compounds, first focused on thermochemic aspects, has been extended to kinetic and mechanistic investigation, owing to the introduction of new experimental approaches such as the radiolytic (66ARP205; 69MI3; 73MI3; 75MI4; 79MI5; 82MI2) and nuclear-decay (70APO79; 75MI5; 82MI2; 83G37) techniques, allowing application of the classical methodology of physical chemistry to gas-phase ionic processes.

Use of simple heteroaromatic molecules as a means of characterizing specific reactivity properties of positive ions, generated in the source of a mass spectrometer, represents the recent prehistory of this field. Thus sparse literature data reveal, among other things that steric hindrance to the gaseous biacetyl cation was evaluated by its reactivity toward encumbered aromatic substrates, including 2-alkylpyridines (73TL4925).

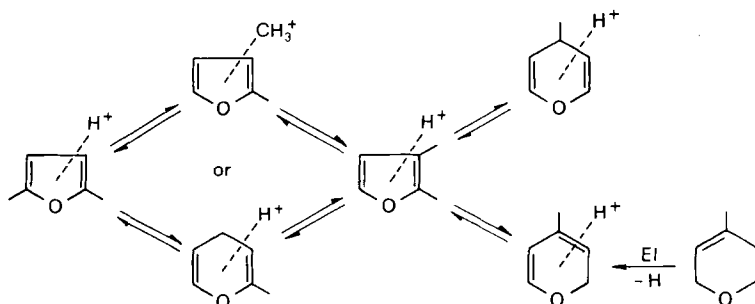
Detailed ICR analysis of the complex reaction pattern induced by the attack of the ions from biacetyl (acetyl, biacetyl, and triacetyl ions) on pyrrole has allowed the demonstration of single and double resonance effects on the abundance of the product ions (72JA6862; 73IJM195). Interestingly, triacetyl cations have been found to be more reactive than biacetyl ions toward pyrrole (rate constants: 11 versus $4.3 \times 10^{-10} \text{ cm}^3 \text{ molecule}^{-1} \text{ sec}^{-1}$), whereas acetyl cations appear unreactive. Furthermore, the rate of the gas-phase reaction of biacetyl cations with pyrrole is only four times as fast as with benzene, in striking contrast with the enormous reactivity difference of the two aromatic substrates measured for a number of electrophilic reactants in solution.

Furan was one of the molecules employed to determine the structure of gaseous C_4H_9^+ ions, generated in the ion sources of an ICR or a collisional activation (CA) mass spectrometer by electron impact on several neutral precursors (Fig. 31). In the ICR studies (74MI3), structures **16–19** display a reactivity toward furan that is in clear disagreement with that observed in the CA analysis (76JA6070). This discrepancy has been attributed to the differences in the internal ion energy (74MI3), which may represent a major

FIG. 31. Some isomeric structures of C_4H_9^+ ions.

drawback of mass spectrometric approaches to structure determination (71ARP527; 74JA6229). In both experiments, however, *tert*-butyl cation **19** displays a very poor reactivity toward furan.

Systematic investigations of the kinetic and mechanistic features of gas-phase, ionic substitutions on simple heteroaromatic compounds first appeared only in the last few years, with the analysis of the fundamental processes of protonation and ethylation of a number of nitrogen aromatic compounds, occurring in their methane chemical ionization mass spectra (80OMS144). Analysis was carried out by the MIKE/CID technique by comparing the fragmentation pattern of the ethylation intermediates with that arising from protonation of standard compounds with an ethyl substituent present in specific positions. Imidazole and benzimidazole appear to undergo protonation and ethylation preferentially at the unsubstituted nitrogen atom. The situation for indazole is less clear, since electrophilic attack on both nitrogen centers cannot be excluded. Pyridine undergoes protonation and ethylation preferentially on the nitrogen atom, whereas pyrrole undergoes carbon substitution, probably at the β positions. While this latter statement agrees with correlations between ionization energies and proton affinities of many nitrogen compounds (63JA2763; 77JA4203), it is nevertheless at variance with the conclusion of an ICR study, concerning the equilibrium proton exchange between deuterated five-membered heteroaromatics and several acceptors [80AG(E)905; 81NJC505; 82MI1]. In this investigation, exclusive α protonation on pyrrole, furan, thiophene, and cyclopentadiene was suggested on the grounds of the extent of deuterium transfer from the heteroarene ion to the acceptor under equilibrium conditions (after 200 msec reaction time). It should be noted, however, that these results provide no direct information regarding the protonation site on the heteroaromatic substrate on account of the very long residence time of the protonated species, which may undergo extensive prototropic rearrangements before structural assay. Profound structural rearrangements have been, in fact, observed between protonated alkylfurans and -pyrans in the gas phase under mass spectrometric conditions via successive ring-enlargement and ring-contraction steps (Scheme 5) (83BSF78; 84TL3815).



SCHEME 5

Application of radiolytic (66ARP205; 69MI3; 73MI3; 75MI4; 79MI5; 82MI2) and nuclear-decay (70APO79; 75MI5; 82MI2; 83G37) methods to the study of the intrinsic reactivity and selectivity of charged electrophiles toward heteroaromatic compounds proved more fruitful than conventional mass spectrometric approaches. Decay and radiolytic methods are, in fact, characterized by a very short lapse of time (10^{-13} – 10^{-9} sec) between the generation of the ionic reactant and its quenching by reactive collision with the substrate. Analysis of the neutral products from the ion–molecule process provides direct information regarding the nature and reactivity of both the ionic reactant and the formed heteroarene intermediate, as well as on their tendency to undergo structural rearrangements.

Ground-state dimethylhalonium ($\text{CH}_3\text{XCH}_3^+$, $\text{X} = \text{F}$ or Cl) and *tert*-butyl ($t\text{-C}_4\text{H}_9^+$) cations, generated in the gas phase by γ radiolysis of the corresponding neutral precursor (CH_3X and *neo*- C_5H_{12} , respectively), were allowed to react with pyrrole, *N*-methylpyrrole, furan, and thiophene under largely different experimental conditions [81CC1177; 82JA7084; 82JA7091; 83JCS(P2)1491]. The most relevant results of these investigations is that gas-phase alkylation of pyrroles, carried out under kinetically controlled conditions (high pressure and high concentrations of an efficient proton acceptor), takes place essentially at the β positions of both substrates (Fig. 32). The

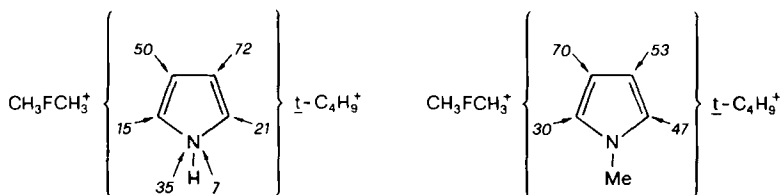


FIG. 32. Positional selectivity of gaseous $\text{CH}_3\text{FCH}_3^+$ and $t\text{-C}_4\text{H}_9^+$ ions toward pyrroles [81CC1177; 82JA7084; 83JCS(P2)1491].

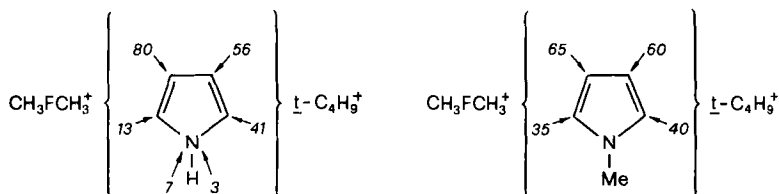


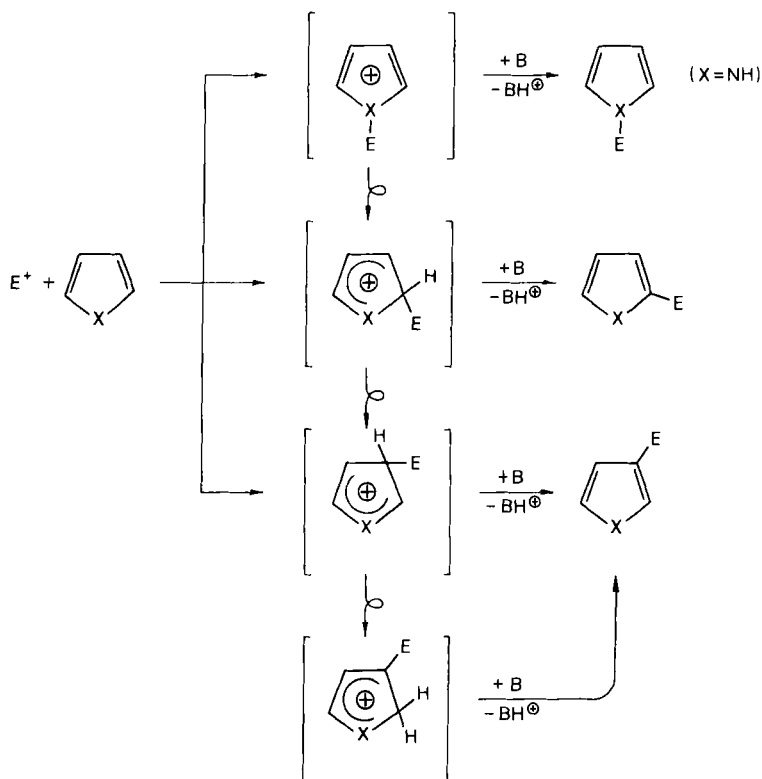
FIG. 33. Isomeric distribution of alkyl substituted pyrroles at low pressure (20–50 Torr) [81CC1177; 82JA7084; 83JCS(P2)1491].

isomeric distribution of the products changes appreciably under conditions favoring thermodynamic control (low pressures and absence of bases) (Fig. 33).

These results are consistent with an alkylation mechanism involving the kinetically predominant attack of the ionic reactant on the β carbons of the pyrrole, followed by isomerization of the primary excited intermediate to the thermodynamically most stable structure **20** (Scheme 6). The apparent increase of α -*tert*-butylation of pyrrole at low pressures reflects the occurrence of alternative reaction paths (protonation, fragmentation, etc.), competitive with alkylation.

On the contrary, alkylation of furan and thiophene by $\text{CH}_3\text{XCH}_3^+$ and $t\text{-C}_4\text{H}_9^+$ ions takes place preferentially at the α carbon or at the heteroatom (Fig. 34). Predominant α substitution in furan ($\alpha:\beta = 2:1$) has been observed as well in the gas-phase methylation by CT_3^+ , generated from β^- decay in CT_4 (82MI5). While the isomeric distribution of *tert*-butylated products is little affected by the experimental conditions, that of the methylated derivatives undergoes significant variations consistent with the general reaction pattern of Scheme 6, which applies to furan and thiophene as well. In contrast with their appreciable positional selectivity, $\text{CH}_3\text{XCH}_3^+$ and $t\text{-C}_4\text{H}_9^+$ ions do not display any significant substrate discrimination, as demonstrated by the intrinsic rate constant ratios shown in Table XIII, measured in competition experiments. This behavior is rationalized on the grounds of most common ion–polar molecule collision theories, which predict that the rate coefficients for reactions between charged electrophiles and organic molecules, with similar dipole moments, fall within the same order of magnitude. The small reactivity differences of Table XIII may be attributed to the different mutual polarization effects between the ionic reactant and the neutral molecule.

The intrinsic directive properties of pyrroles, furan, and thiophene toward alkylating reactants are in satisfactory agreement with those expected on the grounds of the most favorable electrostatic potential path developed in the ion–heteroaromatic encounter pair (72CPL622; 72TCA101; 73CC617; 75T915; 78T275). Accordingly, alkylation is favored at the C_β of pyrroles, at



SCHEME 6

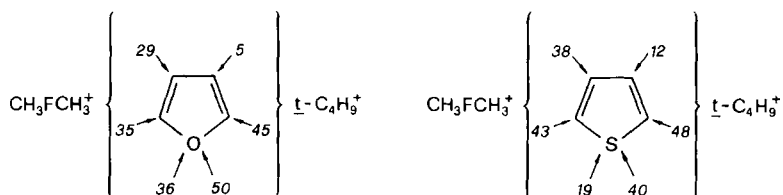



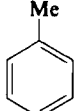



FIG. 34. Positional selectivity of gaseous $\text{CH}_3\text{FCH}_3^+$ and $t\text{-C}_4\text{H}_9^+$ ions toward furan and thiophene [82JA7091; 83JCS(P2)1491].

the heteroatom of furan, and at the C_α of thiophene. In the case of furan, preferential substitution at the C_α sites is favored by the particular structure of the ionic reactant, which is able to "chelate" furan [76CC466; 76JA6492; 77JA4101,5022; 78JCS(P2)891], i.e., to establish preliminary interactions with

TABLE XIII
RELATIVE REACTIVITY OF SIMPLE FIVE-MEMBERED HETEROAROMATIC COMPOUNDS TOWARD
GASEOUS IONIC ELECTROPHILES^a

					
$k_{rel}(\text{CH}_3\text{FCH}_3^+)$	1.7	1.4	1.1	1.0	0.6
$k_{rel}(t\text{-C}_4\text{H}_9^+)$	5.2	2.2	1.0	1.0	1.0
$k_{rel}({}^3\text{HeT}^+)$	1.0	1.3	0.5	1.0	2.0
$\mu(\text{D})(\text{benzene})$	0.71↓	1.92↑	0.52↓	0.36↓	1.80↑
$\mu(\text{D})(\text{gas phase})$	0.66↓	2.12↑	0.55↓	0.36↓	1.84↑

^a Refs. (81CC1177; 82JA7084; 82JA7091; 83JCS(P2)1491; 84JA37).

its most attractive site (the oxygen atom), before attacking the most accessible carbon center (one of the adjacent C_α atoms) (Fig. 35). The same kind of interaction, frequently met in the gas phase by bidentate substrates [76CC466; 76JA6492; 77JA4101,5022; 78JCS(P2)891], can be operative for thiophene as well, although to a much lower extent. When, in fact, the orienting properties of furan and thiophene were determined toward an ionic electrophile without "chelating" properties, such as the ${}^3\text{HeT}^+$ ion, from the β^- decay in T_2 molecules, the tritonation distributions of Table XIV are obtained (84JA37). The reported distributions, while confirming the orienting properties of pyrroles and thiophenes toward alkylating reactants, indicate that a monodentate electrophile, such as ${}^3\text{HeT}^+$, is preferentially directed toward the ring sites of furan (the C_β and the O atoms) developing the most negative electrostatic potential in the encounter pair.

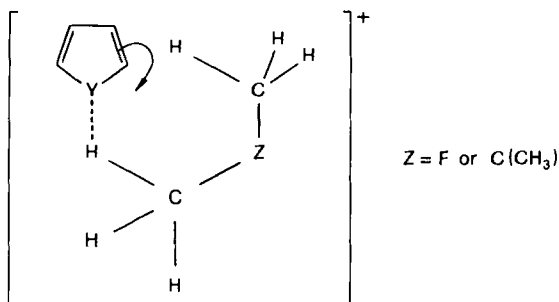


FIG. 35. Electrostatic adduct between furan and gaseous chelating ionic electrophiles [82JA7091; 83JCS(P2)1491; 84JA37].

TABLE XIV
SITE SELECTIVITY OF $^3\text{HeT}^+$ ON SIMPLE FIVE-MEMBERED
HETEROAROMATIC COMPOUNDS^a

Heteroaromatic compound	N (%)	α (%)	β (%)	β/α ratio
Pyrrole	18	37	45	1.2
<i>N</i> -Methylpyrrole	4	40	56	1.4
Furan	—	38	62	1.6
Thiophene	—	82	18	0.2

^aRef. (84JA37).

The experimental data are in good agreement with theoretical predictions based on molecular electrostatic potentials calculated for simple five-membered heteroaromatics. It should be emphasized that the agreement is complete when the experiments are carried out under conditions as close as possible to the ideal ones of theoretical calculations. Thus, for instance, a model considering the interaction of an isolated heteroaromatic molecule with an ionic reactant, such as $^3\text{HeT}^+$, which can be reasonably assimilated to a positive point charge, shows that molecular electrostatic potentials correctly predict site selectivity in heteroaromatic substitution, without requiring arbitrary assumption of multiple N—H or C—H bending out of the molecular plane of the substrate (75T915; 78T275), which are necessary to provide a theoretical rationalization of the data obtained in solution, where the conditions are hardly comparable to those pertaining to the theoretical approach itself.

VI. Summary and Prognosis

From the foregoing, it appears that there has been a tremendous amount of progress in the area of gas-phase heteroaromatic reactivity during the last 10 years. Relatively recent and sophisticated mass spectrometric techniques, such as ion cyclotron resonance, high-pressure mass spectrometry, flowing afterglow, and collisional activation, make it possible to obtain accurate estimates of thermodynamic properties of heteroaromatic compounds in the gas phase. Although still insufficient, these data can be correlated with relevant experimental (ionization potentials, core-electron binding energies, HOMO orbital energies, etc.) and theoretical quantities (protonation energies, charge density distribution, etc.) to provide a unified theory of intrinsic substituent effects on heteroaromatic reactivity. Specific solvation effects on thermodynamic properties of model heteroaromatic compounds can be experimentally tested by means of ion-clustering equilibria measurements

carried out by variable-temperature, high-pressure mass spectrometry and by calorimetric techniques. Detailed kinetic and mechanistic information regarding gas-phase heteroaromatic substitution is made available by radiolytic and nuclear-decay techniques, which provide otherwise inaccessible information regarding basic features of heteroaromatic substitutions, such as intramolecular selectivity, orientation, and steric effects.

Despite the sustained research effort exerted in the last few years in the field, the studies presented here are mainly directed to assessing the intrinsic basicity order of azines and to evaluating their sensitivity to perturbing solvation phenomena. They provide a further justification for the frequent inversion of stability order observed for many organic compounds when going from gas phase to solution, thus representing in principle one of the most important experimental pathways to a general solvation theory. However, in this context, a worrisome lack of balance still remains between generalization of effects derived exclusively from correlations with calculated quantities and those based on experimental thermodynamic data. Besides, these latter mostly pertain to simple substituted azines, whereas other important categories, namely, five-membered heteroaromatic compounds, have been nearly neglected. Finally, only scattered gas-phase acidity data can be retrieved from the literature, thus preventing any generalization of structural and solvation effects.

On the other hand, five-membered heteroaromatic molecules are the model structures first employed for kinetic investigation of the reaction mechanism in gas-phase heteroaromatic substitutions. While comparison of the relevant kinetic data with most common ion-neutral body collision theories and with theoretical predictions appears quite promising, nevertheless, accurate modeling of intrinsic reactivity properties of heteroaromatic compounds demands a more complete research effort, mainly directed to comparing the kinetic behavior of heteroaromatic compounds toward electrophilic and nucleophilic species (83IJM225; 84JOC764) in the gas phase and in solution.

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1,2-Dihydroisoquinolines and Related Compounds

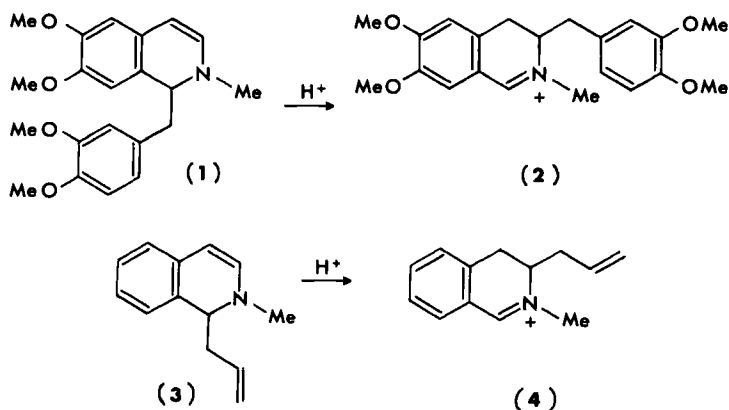
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I. Introduction

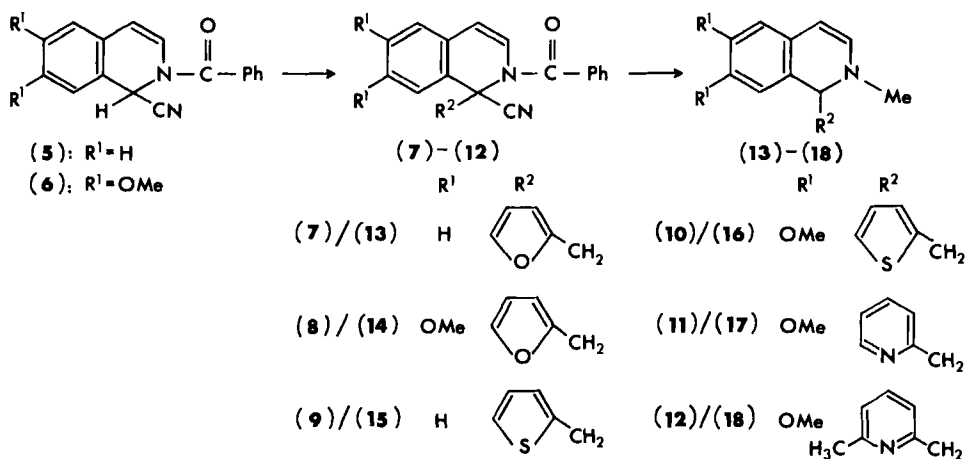
In 1972 Dyke summarized in this series the knowledge of the formation, stability, detection, estimation, and reactions, including rearrangements, of 1,2-dihydroisoquinolines (72AHC279). It was reported that the rearrangement of 2-methyl-1,2-dihydropapaverine **1** to **2**, detected in 1963 in our laboratory and newly called the "Knabe reaction" (84CB1436), occurs as an intermolecular reaction, whereas the rearrangement of the 1-allyl compound **3** to **4** occurs intramolecularly as a [3,3]-sigmatropic aza-Cope rearrangement. In the following years investigations were performed in order to determine the scope and limitations of the 1,2-dihydroisoquinoline rearrangement. Compound **1** was modified by replacing on the one hand the aromatic ring of the benzyl group and on the other the carbocyclic ring of the isoquinoline system by heteroaromatic systems.



II. Syntheses

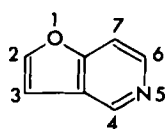
A. 1,2-DIHYDROISOQUINOLINES VIA REISSERT COMPOUNDS

The 1,2-dihydroisoquinolines **13–18**, possessing a heteroaromatic ring system instead of the benzene ring of the benzyl group, are not available by classical syntheses. They were obtained via the anions of the Reissert compounds **5** and **6** (61CI(L)550; 67JHC183), which were substituted with the corresponding halides in the 1 position to form **7–12**, followed by saponification, N-methylation, and reduction with $LiAlH_4$ to give the 1-substituted 1,2-dihydroisoquinolines **13–18** (73AP592; 75AP519; 76AP72).

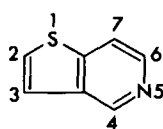


B. FURO- AND THIENODIHYDROPYRIDINES

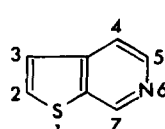
In order to obtain analogs of 1,2-dihydroisoquinolines in which the aromatic carbocycle is replaced by various heteroaromatic systems, the furopyridines (**19**), the thieno[3,2-*c*]pyridines (**20**), and the thieno[2,3-*c*]pyridines (**21**) were synthesized (70BSB301; 71JHC57). By Grignard coupling of 4-chloro-**19** with allylmagnesium chloride in the presence of catalytic



(19)

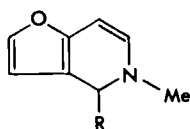


(20)

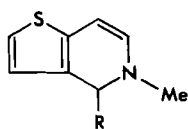


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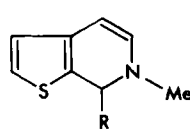
amounts of dichlorobis(triphenylphosphine)nickel(II), 4-allyl-**19** was obtained (58JCS719). After N-methylation and reduction with LiAlH_4 , **22a** resulted (80AP1048). The allyl compounds **23a** and **24a** and the benzyl compounds **22b**, starting from 4-bromo-**19** and **23b**, were synthesized in the same manner with allyl and benzylmagnesium chloride, respectively (73JHC243; 81AP156; 83AP138; 83AP831). The mono- and dimethoxybenzyl substituted compounds **23c**, **23d**, and **24d** were synthesized by Wittig alkylation of 4-chloro-**20** and 7-chloro-**21** with the corresponding (tri-*n*-butyl)benzylidenephosphoranes via the ylides which are transformed to the 4- or 7-substituted compounds **20** and **21**, respectively; then they were N-methylated to the iminium salts and reduced with LiAlH_4 to the desired dihydro compounds **23c**, **23d**, and **24d** (72JA2874; 83AP244; 83AP912).



(22)


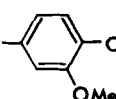


(23)



(24)

(22)/(23)/(24) (a): R = allyl; (22)/(23) (b): R = PhCH_2

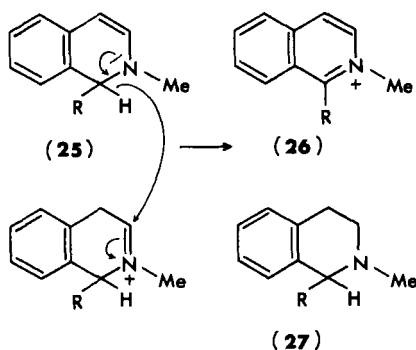
(23) (c): R = CH_2 --OMe; (23)/(24) (d): R = CH_2 --OMe

III. Reactions of 1,2-Dihydroisoquinolines and Related Compounds with Acids

1-Allyl-1,2-dihydroisoquinolines, e.g., **3**, react with acids by an aza-Cope rearrangement to form a 3-allyl-3,4-dihydroisoquinolinium salt, e.g., **4**. The rearrangement of 1-benzyl-1,2-dihydroisoquinolines, e.g., **1**, and related compounds, giving a 3-benzyl-3,4-dihydroisoquinolinium salt, e.g., **2**, depending on the substitution pattern of the starting 1,2-dihydroisoquinoline, is accompanied by disproportionation, elimination, and intramolecular cyclization as side reactions.

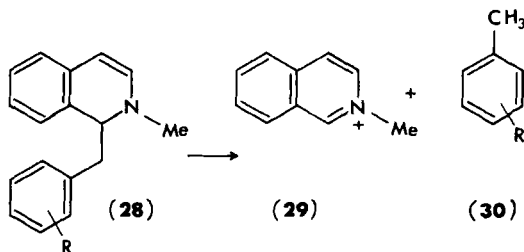
A. DISPROPORTIONATION

When 1,2-dihydroisoquinolines **25** with R = alkyl, phenyl, or styryl are treated with acids disproportionation occurs instead of rearrangement to give an isoquinolinium salt **26** and the corresponding tetrahydroisoquinoline **27** (66AP159; 69TL2107). The disproportionation reaction is considered to be a migration of a hydride ion. Depending on the substitution pattern in such 1,2-dihydroisoquinolines **25**, which are rearranged by acids, the disproportionation reaction can occur to a small extent (71AP52).



B. ELIMINATION

A further reaction of 1,2-dihydroisoquinolines with acids is the elimination of the C-1 substituent. An isoquinolinium salt (**29**) and a toluene derivative (**30**) are formed from (**28**) (70AP255). The reaction can occur if the C-1 substituent is a benzyl or a heteroanalogous benzyl group. In 1,2-dihydroisoquinolines that are able to rearrange, the elimination reaction only is

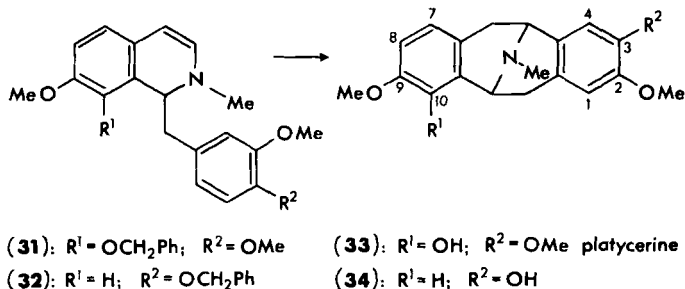


observed to a small extent. It is favored if the C-1 substituent bears negative substituents (70AP255). If the benzyl is replaced by a picolyl group, as shown in 17 and 18, only elimination occurs, this even at room temperature (76AP72).

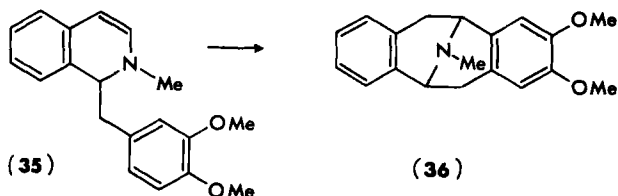
C. INTRAMOLECULAR CYCLIZATION

1. *Pavinanes*

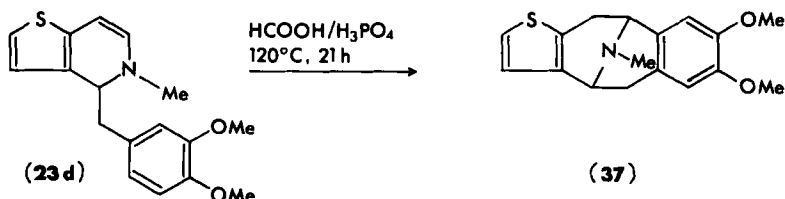
The cyclization of 1,2-dihydroisoquinolines leading to pavinanes has been known for a long time (51LA1; 55JCS2888). It has been found to be a competition reaction of the rearrangement of 1-benzyl-1,2-dihydroisoquinolines, depending on the reaction conditions. Stermitz and Williams have synthesized the pavinane alkaloid platycerine **33** as the racemate in a 60–70% yield by treatment of the 1,2-dihydroisoquinoline **31** with formic and phosphoric acids under reflux (73JOC1761). From the *Papaveracea Argemone munita* subsp. *rotunda*, a new pavinane alkaloid, 2,9-dimethoxy-3-hydroxypavinane (**34**), was isolated. Its structure was confirmed by synthesis of racemic **34**, starting from the 1,2-dihydroisoquinoline **32**. Interestingly enough, when the synthesis was tried via 1-(4-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2-dihydroisoquinoline under conditions favoring pavinanes, then no pavinane cyclization product was formed, but the 3-(4-methoxybenzyl) substituted rearrangement product (73JOC3701) was isolated instead.



Various authors have reported obtaining pavinanes from 1,2-dihydroisoquinolines in better yields, using modified reaction conditions. Walsh and Lyle, for example, added a solution of **35** in chloroform to a mixture of chloroform and 70% aqueous perchloric acid. After stirring for 72 hr at room temperature, the unsymmetrically substituted pavinane (**36**) was obtained in

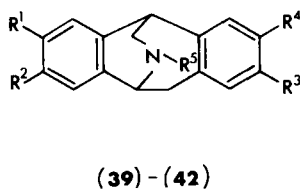
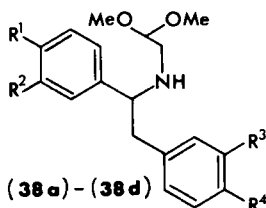


60% yield. The method was also successful in the syntheses of other pavinane derivatives (73TL3849). When the thienodihydropyridine **23d**, a heteroanalogous 1,2-dihydroisoquinoline, was treated for 21 hr at 120°C with a mixture of formic and phosphoric acids, the heteroanalog (**37**) of *N*-methylpavine was obtained in 33% yield (83AP353).

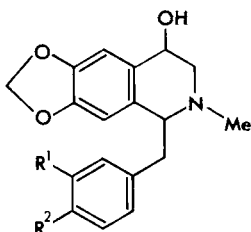
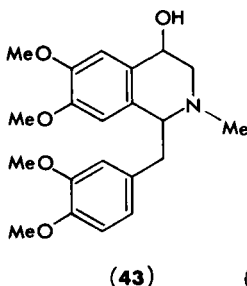


2. Isopavinanes

When the benzylamino acetal **38a** was treated with concentrated hydrochloric acid for 5 days at room temperature, isopavine (**39**) was formed (58JCS1988). By the same procedure **38b** gave norreframidine in 45% yield, and **38c** yielded 40% norreframine. They were *N*-methylated to give reframidine (**40**) and reframine (**41**), respectively (71T3803). Dyke and co-workers have suggested that the conversion of the amino acetals **38** to isopavinanes proceeds via 4-hydroxy-1,2,3,4-tetrahydroisoquinolines as intermediates. 2-Methyl-4-hydroxy-1,2,3,4-tetrahydropapaverine (**43**) was obtained from **1** with diborane, followed by hydrogen peroxide, according to Elliot (67JHC639). When **43** was treated with concentrated hydrochloric acid for 5 days at room temperature, *O*-methylthalisopavine (**42**) was formed in 30% yield (71T3803). As described above, the 4-hydroxy compounds **44** and **45** were obtained from the corresponding 1,2-dihydroisoquinolines. With concentrated HCl/EtOH (6:1) **44** and **45** gave, after concomitant loss of the protec-

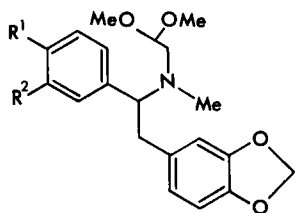


	R ¹	R ²	R ³	R ⁴	R ⁵	
(38a)/(39):	OMe	OMe	OMe	OMe	H	isopavine
(38b)/(40):	O - CH ₂ - O		O - CH ₂ - O		Me	reframidine
(38c)/(41):	OMe	OMe	O - CH ₂ - O		Me	reframine
(38d)/(42):	OMe	OMe	OMe	OMe	Me	O-methyl-thalisopavine



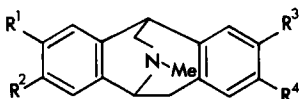
ting benzyl groups, the isopavinanones **48** and **49**, respectively, of which the latter is identical with amurensine (72T3999). From the benzylamino acetal **46**, on treatment with concentrated hydrochloric acid, via the corresponding 4-hydroxytetrahydroisoquinoline, a nonisolable intermediate, the isopavinanone **50**, was obtained. This product is identical with the alkaloid reframoline. The isomeric isopavinanone **51** was obtained in the same manner from the acetal **47** (74T1193).

Umezawa and co-workers have synthesized racemic *O*-methylthalisopavine (**42**) in 92% yield and racemic reframine (**41**) in 90% yield by acid treatment and subsequent methylation of the 4-acetoxytetrahydroisoquinolines **52** and **53**, respectively. The 4-acetoxy compounds **52** and **53** were formed from the corresponding 6-hydroxytetrahydroisoquinolines by lead tetraacetate oxidation in chloroform (73H233). (–)-Reframoline [(–)-**50**] was synthesized, starting from the amine (+)-**54**, via the optically active acetal **55**. Treatment of the latter with hydrochloric acid gave (–)-**50**, $[\alpha]_D^{20} - 144^\circ$ (EtOH), in 16% yield together with 14% (–)-caryachine, (–)-**56**, $[\alpha]_D^{20} - 251^\circ$ (EtOH), a pavinanone alkaloid (78T241). The CD spectrum of (–)-**50** is similar to that



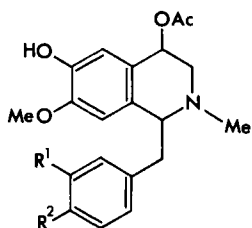
(46): $R^1 = \text{OCH}_2\text{Ph}$; $R^2 = \text{OMe}$

(47): $R^1 = \text{OMe}$; $R^2 = \text{OCH}_2\text{Ph}$



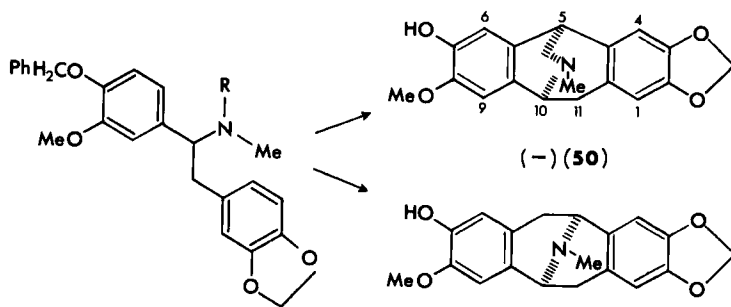
(48) – (51)

	R^1	R^2	R^3	R^4	
(48):	$\text{O}-\text{CH}_2-\text{O}$		OH	OMe	isoamurensine
(49):	$\text{O}-\text{CH}_2-\text{O}$		OMe	OH	amurensine
(50):	OH	OMe	$\text{O}-\text{CH}_2-\text{O}$		reframoline
(51):	OMe	OH	$\text{O}-\text{CH}_2-\text{O}$		



(52): $R^1 = R^2 = \text{OMe}$

(53): $R^1 + R^2 = \text{O}-\text{CH}_2-\text{O}$



(54): $R = \text{H}$

(55): $R = \text{CH}_2-\text{CH}(\text{OEt})_2$

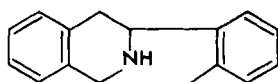
(-)(56)

of (–)-amurensine [(–)-**49**]. The two alkaloids possess the same absolute configuration. The former has been deduced by Shamma *et al.* by an application of the aromatic chirality method, which is being used increasingly in isoquinolines and other systems (67TL3425; 72ACR257; 73T31; 75MI1).

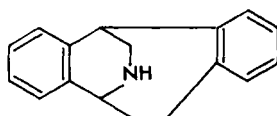
The absolute configuration of (+)-**54**, $[\alpha]_D^{20} + 87.3^\circ$ (EtOH), was deduced to be *S*. Since (+)-**54** gave rise to (–)-reframoline [(–)-**50**] as well as to (–)-caryachine [(–)-**56**], it follows that natural reframoline possesses a 5*S*,10*S* configuration (78T241). The absolute configuration of the pavinane alkaloid (–)-caryachine [(–)-**56**] has previously been established as 5*S*,11*S* by relation with (–)-argemonine of proven configuration [67JCS(C)1317].

3. Homopavinanes and Homoisopavinanes

Homopavinane (**57**) and homoisopavinane (**58**) ring systems represent examples of the phenethylisoquinoline alkaloid class. A synthesis of racemic

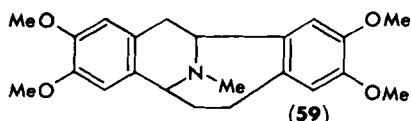


(57)

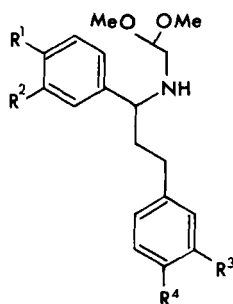
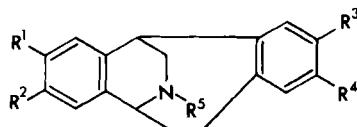


(58)

homoargemonine (**59**), a homopavinane, containing a bicyclo[4.3.1]-azadecane system, has been reported by a method analogous to that used in the preparation of the naturally occurring pavinanes (55JCS2888;



(59)

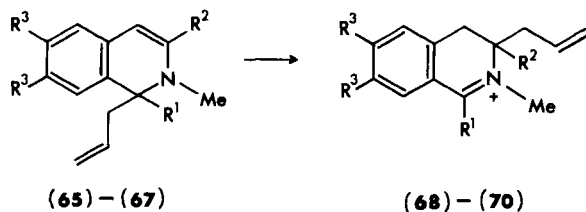
(60): $R^1 = R^2 = R^3 = R^4 = \text{OMe}$ (61): $R^1 = \text{OCH}_2\text{Ph}$; $R^2 = \text{OMe}$; $R^3 + R^4 = \text{O}-\text{CH}_2-\text{O}$ (62): $R^1 = R^2 = R^3 = R^4 = \text{OMe}$; $R^5 = \text{H}$ homoargemonine(63): $R^1 = R^2 = R^3 = R^4 = \text{OMe}$; $R^5 = \text{Me}$ (64): $R^1 = \text{OH}$; $R^2 = \text{OMe}$; $R^3 + R^4 = \text{O}-\text{CH}_2-\text{O}$; $R^5 = \text{H}$

73JOC2099). Syntheses of derivatives of the hitherto unknown homoisopavinane ring system, containing a bicyclo[4.2.2]azadecane system, were described by Dyke and Warren (79T1857). Starting with the amino acetal derivative **60** under conditions used successfully for the preparation of isopavinanones, the homoisopavinane **62** was obtained in 39% yield. It was methylated to **63**. The acid-catalyzed cyclization of the amino acetal **61** gave a mixture of components, from which the phenolic homoisopavinane **64** was isolated (63%).

D. REARRANGEMENTS

1. 1-Allyl-1,2-dihydroisoquinolines and Related Compounds

1-Allyl-2,3-dimethyl-1,2-dihydroisoquinoline (**65**) does not rearrange to a 3-allyl-2,3-dimethyl-3,4-dihydroisoquinolinium salt (**68**) when treated with dilute hydrochloric acid, but the introduction of a methyl group in the 1 position leading to **66** or of methoxy groups in the 6,7 positions to give **67** enables the reaction to proceed to **69** or **70**, respectively (73T4303). Kinsman

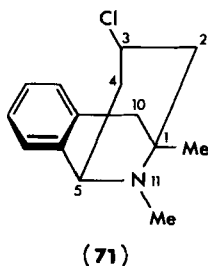


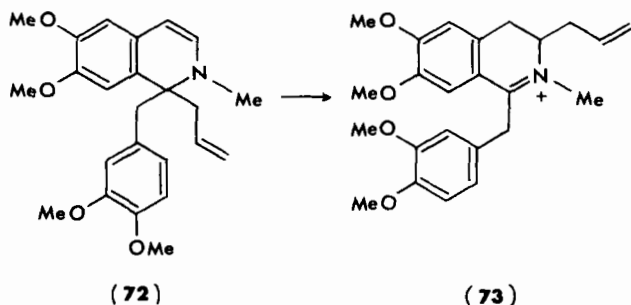
(65)/(68): $R^1 = R^3 = H$; $R^2 = Me$

(66)/(69): $R^1 = R^2 = Me$; $R^3 = H$

(67)/(70): $R^1 = H$; $R^2 = Me$; $R^3 = OMe$

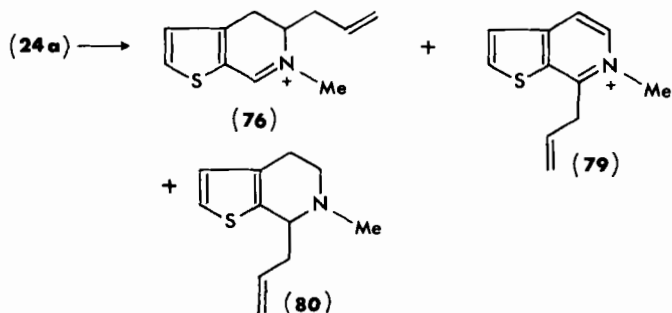
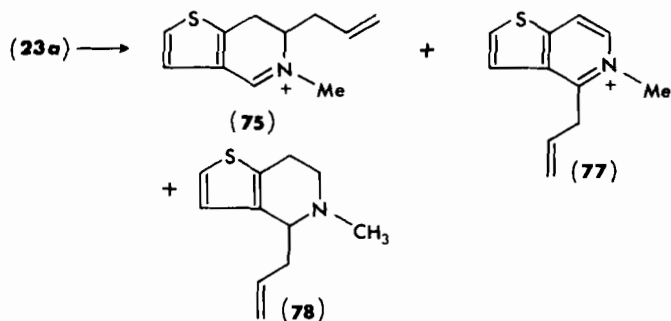
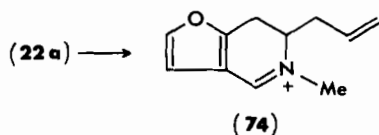
and Dyke found that **65**, when heated under reflux for 10 days with 2 *N* HCl gave 3-chloro-11-azabenzof[*f*]bicyclo[3.3.1]nonane (**71**) in high yield (75TL2231). 1-Allyl-2-methyl-1,2-dihydropapaverine (**72**) is rearranged by





dilute acids exclusively to the iminium salt **73** (71T6181). This shows that in a 1-substituted 1,2-dihydroisoquinoline, where it is possible for either a dimethoxybenzyl group or an allyl group to migrate, the latter does so with practically complete exclusion of the former.

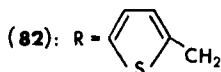
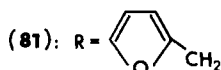
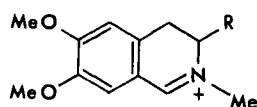
The furo- (**22a**) and thienodihydropyridines (**23a** and **24a**) rearrange in acidic solution to the iminium salts **74** (80AP1048), **75** (83AP138), and **76**



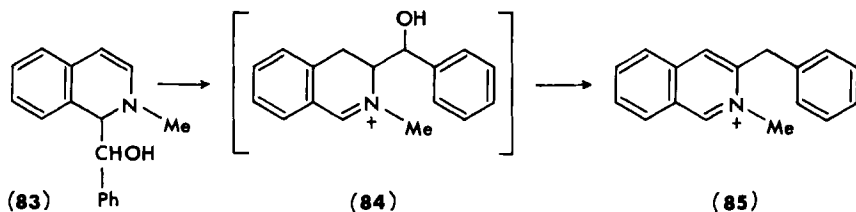
(83AP831). Product **74** was obtained in only 10% yield, and a considerable part of the starting material (**22a**) was found to be resinified under the acidic conditions. The iminium salts **75** and **76** form in 23 and 49% yields, respectively. In both cases, disproportionation products could be isolated: from **23a** the compounds **77** and **78** in low yields and from **24a** the compounds **79** and **80** in yields of about 15%. These findings demonstrate that the furo-(**22a**) and thienodihydropyridines (**23a** and **24a**) under the rearrangement conditions behave similarly to the corresponding 1-allyl-1,2-dihydroisoquinolines.

2. 1-Benzyl-1,2-dihydroisoquinolines and Related Compounds

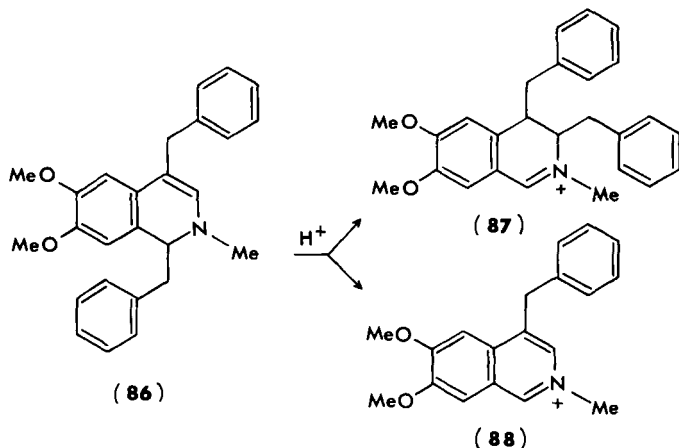
The rearrangement of 1-benzyl-1,2-dihydroisoquinolines and related compounds is easier when they possess one or two methoxy groups in a 6 and/or 7 position. Compound **14**, possessing two OMe groups, rearranges with acids to the 3,4-dihydroisoquinolinium salt **81** (72%), and **16**, also possessing two OMe groups, gives 67% of **82**. From the 1,2-dihydroisoquinolines **13** and **15**, where the OMe groups in the 6 and 7 positions are missing, the yield of rearrangement product is very low, and many side reactions occur (73AP592).



The dihydroisoquinoline **83** gave with 2 N HCl the isoquinolinium salt **85**, which was formed under the reaction conditions from **84** by dehydration, followed by aromatization (73AP648). Compound **86**, having benzyl groups in



both the 1 and 4 positions, rearranges to **87**, but the yield is only 15%. Moreover, 40% of **86** is recovered after 1 hr of heating on a water bath along with about 40% of the elimination product **88** (70MI1). The yield of rearrangement product is diminished if the *N*-methyl group is replaced by a more bulky substituent. In all compounds examined, elimination and disproportionation occur as side reactions (71AP52).

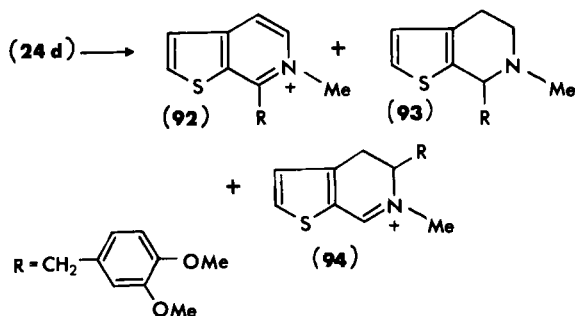
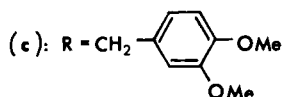
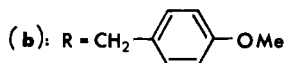
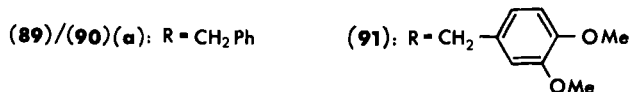
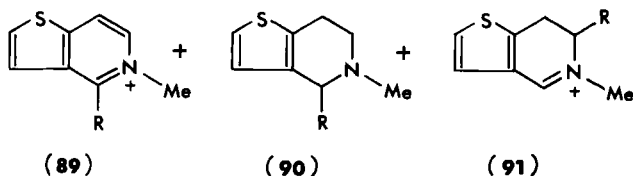
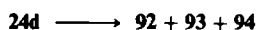
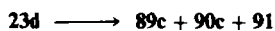
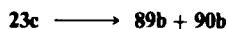
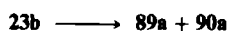


In 1972 in our laboratory a standard procedure for the rearrangement of 2-methyl-1,2-dihydropapaverine (**1**) was elaborated (73AP784). The highest yields of rearrangement product were obtained using water/ethanol (1:1)/1 *N* HCl (4:1 to 1:1) as solvent, corresponding to a 0.1–0.5 *N* acid. A dihydroisoquinoline concentration of 2%, and a reaction temperature of 60°C were used. The most important parameters are the solvent and the concentrations of the acid and of the dihydroisoquinoline. With diminishing concentration of **1**, the yield of rearrangement product decreases from 82 to 7% at a 0.1% concentration.

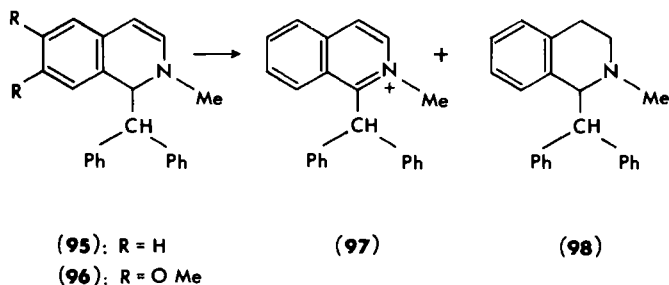
The 1-benzylfuro- (**22b**) and 1-benzylthieno-1,2-dihydropyridines (**23b**, **23c**, **23d**, and **24d**) were treated with acid under the described standard conditions with the following results:

- 22b**: no rearrangement, and no definable reaction products (81AP156);
- 23b**: no rearrangement, 10% disproportionation to **89a** and **90a**;
- 23c**: no rearrangement, 10% disproportionation to **89b** and **90b**;
- 23d**: rearrangement to **91** in 30% yield, 7% disproportionation to **89c** and **90c** (83AP244);
- 24d**: rearrangement to **94** in 6% yield, 8% disproportionation to **92** and **93** (83AP912).

A considerable part of each of the starting compounds **22b** to **24d** was found to be resinified under the acidic reaction conditions.

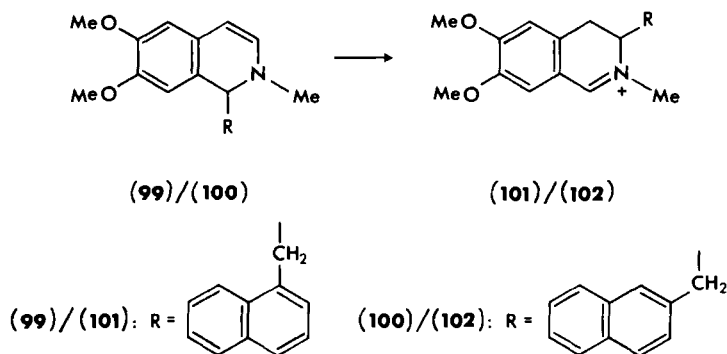


In order to determine the scope and limitations of the rearrangement of 1-benzyl-1,2-dihydroisquinolines with acids (Knabe reaction) the behavior of some model compounds was examined, especially compounds possessing a bulky substituent in the 1 position. In this connection the reaction of the dihydroisquinoline **95** was studied. Surprisingly, **95** did not rearrange under rearrangement conditions. The disproportionation products **97** and **98** were isolated in a yield of 55%, after 8 hr, and 27% of unchanged **95** was also recovered (72UP1). Possibly the absence of methoxy groups in the 6 and 7

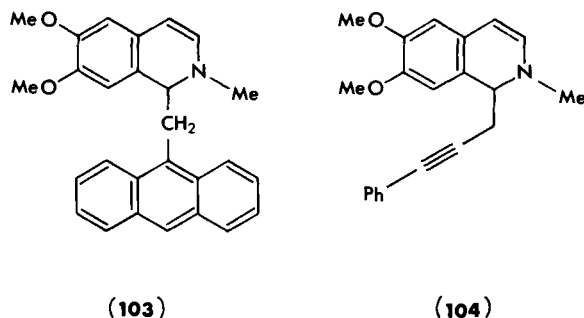


positions in **95** caused the failure of the rearrangement. Therefore, compound **96** is to be synthesized and to be treated with dilute HCl (86UP3).

From the corresponding isoquinolinium salts, synthesized for the first time, the dihydroisoquinolines **99** and **100** were obtained as usual. When treated under standard conditions with hydrochloric acid, the compounds **99** and **100**

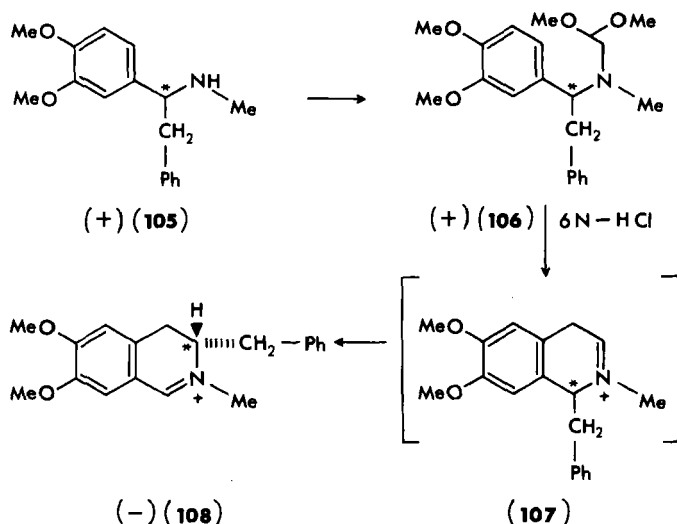


rearrange to the iminium salts **101** and **102**, respectively, in yields of about 50% (86UP1). Subsequently, compound **103** was synthesized by classical methods in order to study its behavior toward acids (86UP1).



Some years ago in our laboratory it was found that a 1-cinnamyl-1,2-dihydroisoquinoline reacted as a vinylogous 1-benzyl compound under the rearrangement conditions to give the expected 3-cinnamyl-3,4-dihydroisoquinolinium salt in 80% yield (70AP404; 71T6181). Now we are testing whether the 1-phenylpropargyldihydroisoquinoline **104**, which can be obtained via different pathways, rearranges with dilute acids as an ethynyl analog of a 1-benzyl compound (86UP2).

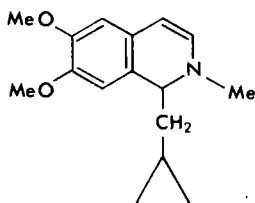
In order to study the stereochemical course of the rearrangement of 1-benzyl-1,2-dihydroisoquinolines, the optically active acetal (+)-**106** was synthesized, starting with the amine (+)-**105**. Compound (+)-**106** is a precursor of an optically active 1-benzyl-1,2-dihydroisoquinoline possessing an asymmetric center in the 1 position. The ring closure of the acetal (+)-**106**, performed with 6 *N* HCl, leads to 1,2-dihydroisoquinolines or, in compounds that can be rearranged under acidic conditions, via **107** to the 3-substituted 3,4-dihydroisoquinolinium salt **108** [64CI(L)1950; 65JOC2247; 69T101]. The 3,4-dihydroisoquinolinium salt (–)-**108** is obtained from (+)-**105** in 47% yield. The perchlorate of (–)-**108** shows the specific rotation $[\alpha]_D^{22} -161.3^\circ$ in acetonitrile (73AP784). This experiment shows that the rearrangement of 1-benzyl-1,2-dihydroisoquinolines occurs stereoselectively or stereospecifically. In order to determine the absolute configuration of the amine (+)-**105**, it was decomposed to optically active compounds of known configuration. Accordingly, for (+)-**105** the *S* configuration was deduced. The rearrangement product (–)-(**108**), also possesses the *S* configuration. This result was obtained



by the synthesis of (–)-**108**, starting from optically active substances of known configuration (79AP273). These findings of the chemical correlations were confirmed by chiroptical methods (79AP492).

IV. Mechanism of the Rearrangement of 2-Methyl-1,2-dihydropapaverine

The rearrangement of 1-benzyl-1,2-dihydroisoquinolines by acids occurs intermolecularly, as shown by crossing experiments (66CB2873; 75T449). This result was confirmed by the strong dependency of the rearrangement on the enamine concentration (73AP784). The following possibilities can be discussed for the mechanism: (a) elimination of the migrating benzyl group as an ion or radical and migration to a second molecule that itself loses or has lost a benzyl group, or (b) a synchronous bimolecular exchange reaction during which two molecules exchange their benzyl groups. As shown above, the rearrangement occurs stereoselectively or stereospecifically. In many experiments it was possible to detect neither a radical intermediate by ESR spectroscopy nor a CIDNP effect in the NMR spectra (69UP1; 79T857). Therefore a radical mechanism seemed to be improbable. A cationic course of the rearrangement was excluded because the 1-cyclopropylmethyl-1,2-dihydroisoquinoline (**109**), which should be able to form a relatively stable

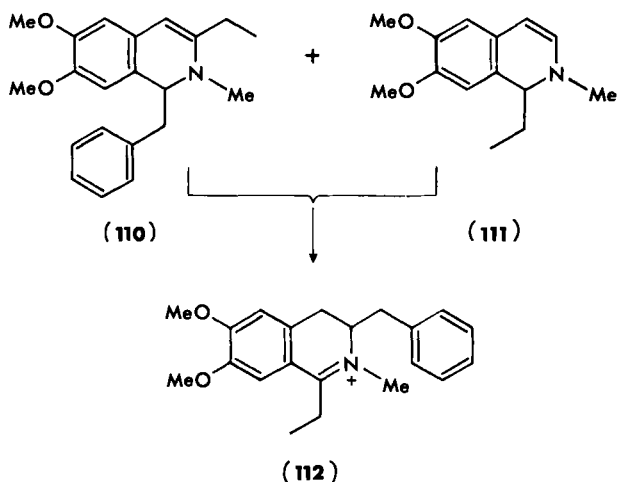


(**109**)

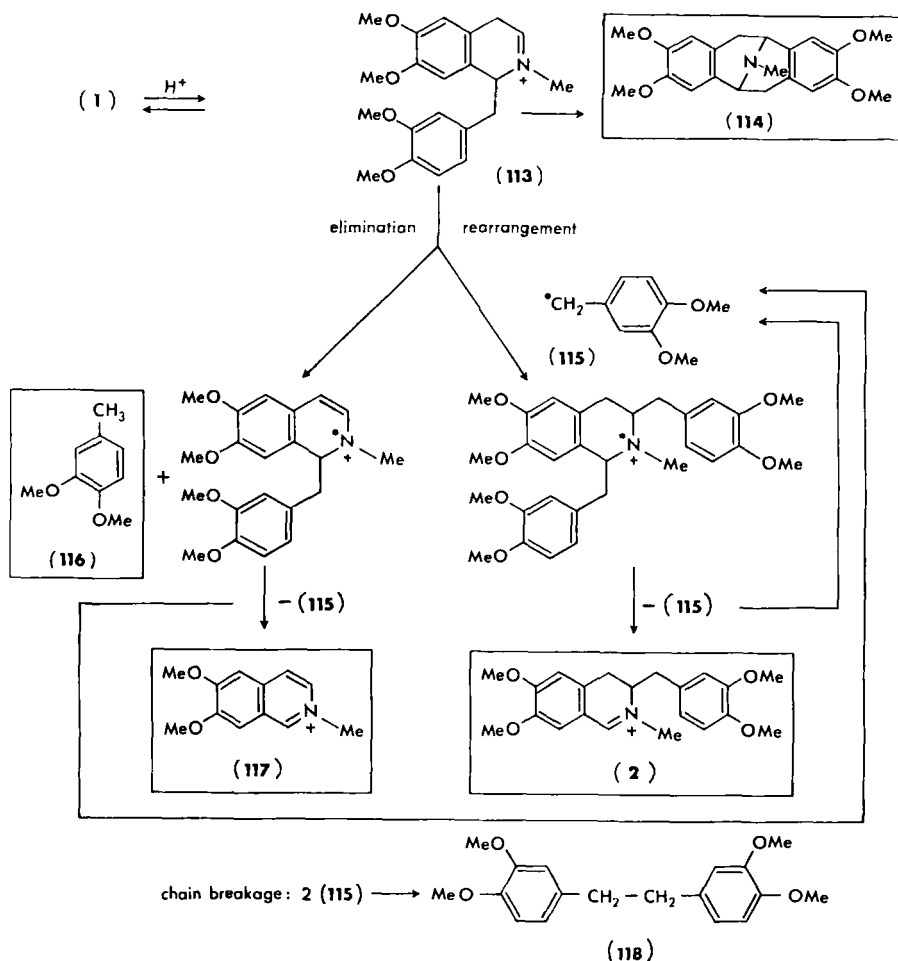
cyclopropylmethyl cation, on treatment with dilute acid only gave disproportionation (74AP727). The transformation of optical activity from **105** to **108** was a strong indication that the rearrangement occurred via a synchronous mechanism (72TL5373; 73AP784; 75T449). But the finding that *S*-(–)-**108** was formed from *S*-(+)-**105** shows the rearrangement to run antarafacially and not suprafacially, as necessary for the supposed synchronous mechanism. Therefore a modified mechanism was proposed comprising the formation of ion pairs in an anionic chain reaction, causing an antarafacial stereospecific S_N2' reaction (80AP1033). The proposed mechanism, which integrates the elimination reaction of a benzyl anion as starting reaction, was compatible

with all findings concerning the rearrangement of 1-benzyl-1,2-dihydroisoquinolines.

In order to demonstrate the transfer of a benzyl group to an acceptor under the rearrangement conditions, a mixture of the 1-benzyl-3-ethyl-1,2-dihydroisoquinoline **110**, a 3-substituted 1,2-dihydroisoquinoline that does not rearrange, and the 1-ethyl-1,2-dihydroisoquinoline **111**, which normally gives disproportionation, was treated with dilute acid. The 3,4-dihydroisoquinolinium salt **112** was obtained in 5% yield. This experiment demonstrated that the transfer of a benzyl group from a 1,2-dihydroisoquinoline (**110**), existing as a 1,4-dihydroisoquinolinium salt in acidic solution, to form the 3,4-dihydroisoquinolinium salt **112** is possible. The low yield of **112** can be



explained by noting that under these conditions the chain reaction does not occur. The structure of **112** has been confirmed by an independent synthesis (80AP1033). Rüchardt was in doubt as to whether benzyl anions as ion pairs could exist in acidic aqueous solution without spontaneous protonation. In view of the newer radical chemistry and the participation of benzyl radicals in addition reactions to electron-poor π systems, he favored a radical chain reaction for the rearrangement of 2-methyl-1,2-dihydropapaverine (**1**) and the accompanying elimination reaction, which leads to **116** and the isoquinolinium salt **117**. 3,4-Dimethoxybenzyl radicals **115** were formulated to be the chain-carrying species (84CB1436). In the chain-termination step two radicals **115** combine to form the compound **118**. The radical chain reaction could be inhibited by the addition of tribromoacetic acid. Another active inhibitor of the rearrangement of **1** was found to be 3-cyanopyridine, which reacts quickly with benzyl radicals (77JA7960). *N*-Methylpavine (**114**) is formed in dilute solution or when **1** is treated with concentrated hydrochloric acid (73AP784).

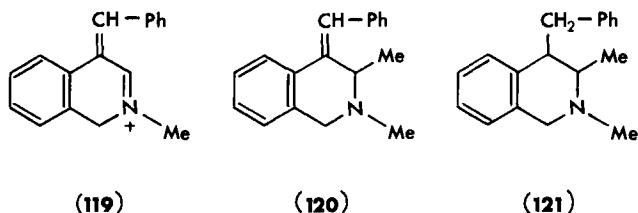


The lack of ESR signals and of the CIDNP effect can be explained by the existence of radicals only in a very low concentration in the radical chain (84CB1436).

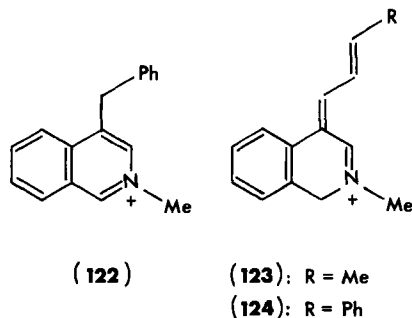
V. Syntheses with 1,2-Dihydroisoquinolines

In Section III,C it was shown that various 1-substituted 1,2-dihydroisoquinolines can be cyclized intramolecularly to give pavinanes, isopavinanes, homopavinanes, and homoisopavinanes. Section III,D deals with the formation of 3-substituted isoquinoline derivatives from 1-allyl-, 1-benzyl-1,2-dihydroisoquinolines, and related compounds. In this section some synthetic reactions of 1,2-dihydroisoquinolines are reported.

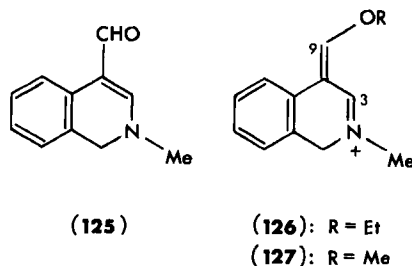
The course of the condensation reaction between 1,2-dihydroisoquinolines and aromatic aldehydes in acidic solution has been defined by Dyke and co-workers by the isolation and characterization of 4-benzylidene-1,4-dihydroisoquinolines (**119**) and reported to be in press (72AHC279); in the meantime the paper has appeared (71T4532). The structure of compound **119** was confirmed by reaction with methylmagnesium iodide. The tertiary base **120** was formed; it was hydrogenated catalytically to give **121**. Compounds **119**

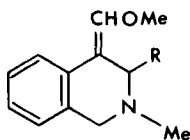


are easily isomerized to the 4-benzylisoquinolines **122** by acids or bases. The products obtained by the acid-catalyzed reaction between 2-methyl-1,2-dihydroisoquinoline and crotonaldehyde or cinnamaldehyde were **123** or **124**, respectively (71T4532).



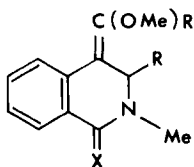
Treatment of 4-acyl-1,2-dihydroisoquinolines, e.g., **125**, with triethyloxonium tetrafluoroborate (Meerwein reagent) produced vinylogs of the ethoxyiminium cations in high yield, e.g., **126**. Crystallization of **126** from methanol gave pure **127**. In order to perform syntheses of 3-substituted





(128): R = Ph

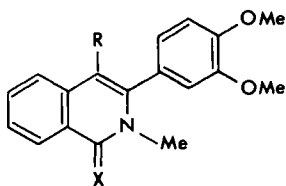
(129): R = Et

(130): R = CH₂ Ph(131): R = CH₂ Ph; X = 2 H

(132): R = CN; X = 2 H

(133): R = CN; X = O

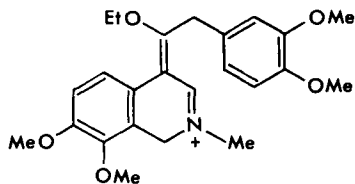
isoquinoline derivatives, some reactions of these salts with nucleophilic reagents were useful. With phenyl- or ethylmagnesium bromide, the compounds **128**, in 82% yield, and **129** were obtained; with benzylmagnesium bromide, the compound **131** having two benzyl groups, was isolated in 40% yield. With restricted amounts of Grignard reagent, the reaction gave the expected product **130**. With KCN, a mixture of **132** and **133** was obtained. These results show that nucleophiles can attack **128** either at C-3 or at C-9, followed by further reaction pathways (79T1861). Reduction of **134** with LiAlH₄ gave the 1,2-dihydroisoquinoline **135** from which **136** was formed by the Vilsmeier reaction in 83% yield.



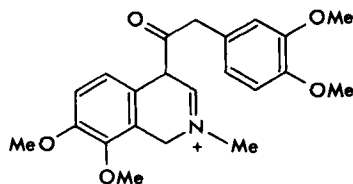
(134): R = H; X = O

(135): R = H; X = 2 H

(136): R = CHO; X = 2 H

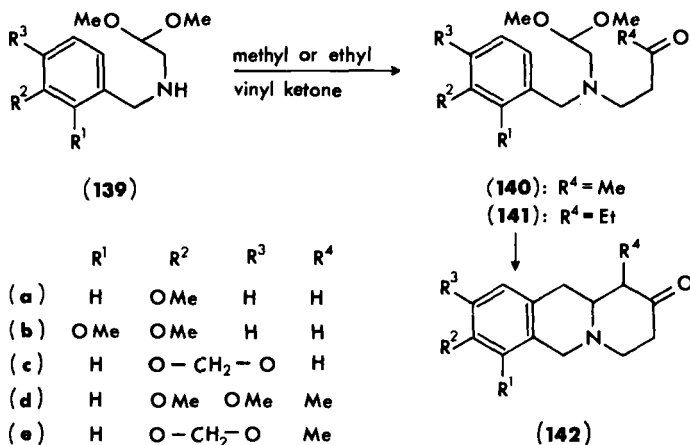


(137)



(138)

Attempts to achieve the thermal ring closure of the Meerwein salt **137** to the benzo[*c*]phenanthridine system failed; the major product was the 4-acylisoquinolinium salt **138** (79T1861). The reaction between *N*-benzylaminoacetaldehyde dialkyl acetals (**139**) with methyl vinyl ketone in acidic solution, leading to benzo[*b*]quinolizine derivatives, was newly investigated. The



structures of the reaction products have been confirmed, the scope of the reaction broadened, and the conformation of the products determined (83AJC149). In addition to some benzoquinolizines prepared previously by Bobbitt and Moore (63JOC2958), the benzoquinolizidine derivatives **142a-c** and, by reaction of **(139)** with ethyl vinyl ketone, the compounds **142d-e**, via the intermediates **140** and **141**, were synthesized. In all cases the compounds **142** in their IR spectra show strong Bohlmann bands, demonstrating that they all possess a *trans*-quinolizidine system.

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4-Amino-1,2,3-triazoles

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I. Introduction and Nomenclature

From the discovery of the first 1,2,3-triazole by Hans von Pechman in 1888 to the present time, interest in these substances has expanded exponentially, and the subject now commands a vast literature. In this series, the subject has not been covered since 1974 [74AHC(16)33], but a recent review by H. Wamhoff provides a good, broad coverage [84CHC(5)669], which is usefully supplemented by two books: K. Finley's monograph (80MI1), and a collaborative volume on all the azoles (76MI1). The present review, which is confined to the *C*-amino derivatives of 1,2,3-triazole, describes these in more depth than was possible in the general reviews.

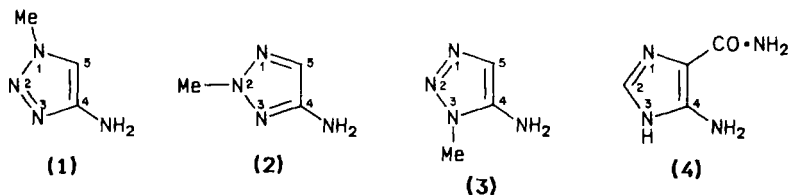
The 4-aminotriazoles are of special interest because of the following properties. The amino group attenuates, by electronic release, the normally π -deficient character¹ of the triazole nucleus. A strong bathochromic shift in the UV spectrum is evident (Table II). This 4-amino group introduces the possibility for ring opening, followed by closure to isomers, often 4-alkylaminotriazoles, which would be difficult otherwise to synthesize (Section III,C). This process, known as the Dimroth rearrangement, can advantageously be reversed to avoid use of the dangerous reagent methyl azide².

In combination with a suitable group in the 5 position, the 4-amino group permits annelation of a new ring on to the triazole ring. It is exceedingly useful to be able to make any 4,5-disubstituted triazole required for generating such bicyclic systems. In the past, this has not been easy because the nonsymmetrical placement of the 4-amino group complicates the synthesis whenever (as frequently happens) an alkyl group is required on a particular ring-nitrogen atom, because three isomers (e.g., 1, 2, and 3) have to be considered. Suitable intermediates in the 3-alkyl series have long been available, but in the other two series only since 1968 [68JCS(C)344; 68JCS(C)2076] (see Section III,A,1).

4-Amino-1,2,3-triazole analogs of 4-aminoimidazole-5-carboxamide (4), which is a necessary intermediate for the synthesis of purines in all forms of life, have proved to be valuable inhibitors in experimental biology (see Section V).

¹ The terms π -deficient and π -excessive were introduced by the author in 1953 [53CI(L)1171] to provide a more satisfactory classification than then existed for the main types of heterocyclic nuclei. In 1959, this classification was elaborated as a book (59MI1).

² For more on tautomerism in this series, see Section III,C.



For numbering the 1,2,3-triazole ring, IUPAC rules provide little guidance. *Chemical Abstracts* assigns No. 1 to that nitrogen atom (at the end of the N—N—N sequence) from which three single bonds radiate. This author has found it a considerable advantage to keep the number of a *carbon* substituent constant. In this review, the C-amino group will always be allotted the 4 position; the numbering of substituents attached to a ring-nitrogen atom follows from this. The author has used this system successfully for many years in his papers in the *Journal of the Chemical Society*. Hence, the present review will refer to **1** as 4-amino-1-methyl-1,2,3-triazole, to **2** as 4-amino-2-methyl-1,2,3-triazole, and so on. As the *N*-alkyl substituent and the “indicated hydrogen” will always have the same number, no use of [1*H*], etc., will be made here.

Any diminution in stability or aromaticity suggested by the bonding in **2** (compared to **1** and **3**) is not evident in the handling of **2** and its derivatives nor in their physical properties, which do not differ greatly from those of their isomers. The primary amino group is 4-aminotriazole and its derivatives does not seem to be in equilibrium with any measurable proportion of an imino tautomer.

The CAS ONLINE program

STR GRA R5,4 C1, NOD 1 2 3 6 N, RSP I, END

brought to light 1461 compounds closely related to 4-amino-1,2,3-triazole and contained in 283 references.

II. Structure and Physical Properties

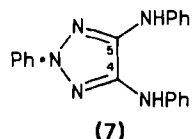
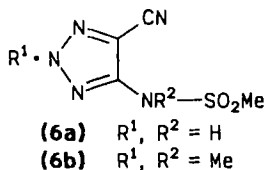
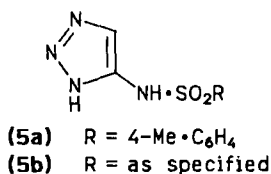
The proportion of tautomers in 1,2,3-triazole (the parent molecule), as ascertained by ¹H NMR (300 MHz), has been found to vary with concentration, temperature, and solvent [84JCS(P2)1025]. No similar study has been made of the 4-amino-1,2,3-triazoles, but crystallographic studies (see Section II,A) have revealed preferred sites of attachment of the ring-bound mobile hydrogen atom. However, crystal studies do not necessarily indicate the equilibria attained in solution. NMR and UV spectra of **5a** revealed the presence of three tautomers, the proportions of which depended on the polarity of the solvents (75G583) (no assignments were made).

A. CRYSTALLOGRAPHY; ELECTRON DENSITY; DIPOLE MOMENTS

X-Ray crystal diffraction study of 4-amino-1,2,3-triazole-5-carboxamide, a much-used intermediate, assigned the mobile hydrogen atom to N-3. The molecule was planar, and molecules were linked as dimers by hydrogen bonding of the amide group of one molecule to the N-1 of the next. These dimers were further linked by a complex three-dimensional network of hydrogen bonds. The compactness of this structure is attested by the high density (D_m 1.629 g cm⁻³) of the crystals [74JCS(P2)1849]. The corresponding ester, 4-amino-5-ethoxycarbonyl-1,2,3-triazole, is flat and has the mobile hydrogen atom on N-3; but the molecules are much less hydrogen bonded to one another [77AX(B)3102]. The 3*H* tautomer was favored also in the cupric chloride complex of 4-amino-1,2,3-triazole-5-carboximidine (75JA2376). However, crystal studies showed that the 2*H* tautomer was favored in 4-mesylamino-1,2,3-triazole-5-carbonitrile (**6a**). The unusual structure did not affect established lengths of the ring bonds [76AX(B)2245].

When treated with methyl iodide, **6a** gave **6b**, the dimensions of whose (planar) ring were identical with those of **6a**. However, the exocyclic methyl substituent had twisted (by 124°) the bond that united the *N*-mesylamino group to the nucleus, and the nitrile group was now "considerably bent" out of the plane of the triazole ring. Moreover, the bond between the mesylamino group and the triazole ring was longer than in **6a**; indicating a looser binding of the side chain [77AX(B)3097].

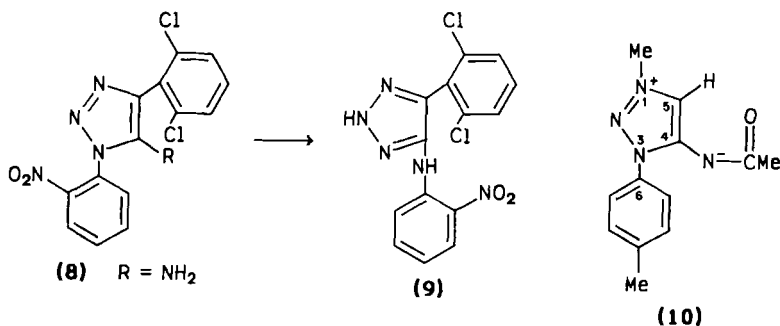
Comparing these examples, the Hungarian crystallographers noted that the bond angle enclosing N-2 is 116° in 2*H* (and 108° in 3*H*) examples and that the angle enclosing N-3 is 103° in 2*H* examples but varies from 108 to 111° in 3*H* examples [77AX(B)3102]. Mutual steric interference of substituents in the 4 and 5 positions was demonstrated in crystal studies of 2-phenyl-4,5-dianilino-1,2,3-triazole (**7**), although the molecule was symmetrical. The chemically equivalent 1-2 and 2-3 bond distances were found to be 1.312 and 1.379 Å, respectively. Whereas the 4-anilino group was almost coplanar with the triazole ring, the 5-anilino group was nearly perpendicular [77AX(B)3423].



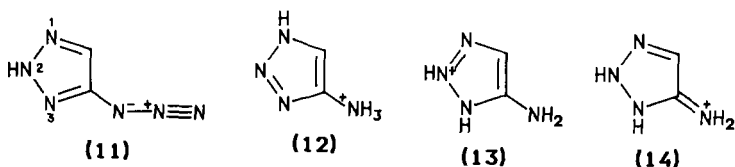
The 4-amino-3,5-diphenyltriazole **8** was found to have no unusual bond angles or distances, and the three rings were coplanar. Hence the Dimroth rearrangement (to **9**), which occurred on heating **8** to 200°C, owed nothing to

steric strain. It is noteworthy that the two benzene rings in **9** are tilted with respect to the triazole ring, and the nitro group is rotated with respect to the relevant benzene ring [84AX(C)1901]. (For more on Dimroth rearrangements, see Section III,C.)

Bond lengths, found in a crystal study of the mesionic compound **10**, were in good agreement with CNDO/2 calculations. Steric interaction between the benzene ring and the acetimidate group caused deformation of the N-2-N-3-C-6 and the C-4-N-3-C-6 angles; also the triazole and benzene rings were not coplanar [83AX(C)1581].



The dipole of 4-azidotriazole, a compound related to 4-aminotriazole, was found to be 2.35 D (in dioxane, 25°C) and was compared to 4.46 D for the parent 1,2,3-triazole. It was concluded, after comparative studies with other azido compounds, that the predominating tautomer was HN-2 (11). Whether the azido group is oriented mainly *Z* or *E* was not experimentally determined, but CNDO calculations indicated the *Z* form, i.e., the one with the azido group turned toward the nearest ring-nitrogen atom (N-3) (78BSB189). For the use of ^1H NMR to assign *cis* and *trans* structures, see Section II,D.



B. IONIZATION IN WATER

The absence of covalent hydration [65AHC(4)1; 76AHC(20)117] enables the ionization constants and UV spectra of 1,2,3-triazoles to be interpreted more readily than those of 8-azapurines (1,2,3-triazolopyrimidines), which exhibit this phenomenon strongly [86AHC(39)117]. Table I presents the

TABLE I
REPRESENTATIVE IONIZATION CONSTANTS OF 1,2,3-TRIAZOLES IN WATER AT 20°C

Substance	pK _a		Reference
	As base	As acid	
1,2,3-Triazole	1.17	9.42	63PMH(1)98
1-Methyl	1.25	—	63PMH(1)98
2-Methyl	— ^a	—	—
4-Amino-1,2,3-triazole			
(Unsubstituted)	2.39	9.47	85MI1
5-Acetamidomethyl-3-benzyl	1.00	—	73JCS(P1)1634
5-Acetamidomethyl-1-methyl	2.19	—	73JCS(P1)1634
5-Amidino [C(=NH)NH ₂]	6.38 ^b	12.23 ^c	74JCS(P1)2030
5-Aminocarbonyl (CONH ₂)	-0.23	7.79	68JCS(C)344
5-Aminocarbonyl-1-methyl	0.69	—	68JCS(C)344
5-Aminocarbonyl-2-methyl	0.10	—	68JCS(C)2076
5-Aminocarbonyl-3-methyl	— ^d	—	68JCS(C)2076
5-Aminomethyl-3-benzyl	-0.45; 8.85	—	73JCS(P1)1634
5-Aminomethyl-1-methyl	1.01; 7.65	—	73JCS(P1)1634
5-Aminomethyl-2-methyl	0.70; 8.58	—	73JCS(P1)1634
3-Benzyl	1.78	—	70JCS(P1)230
3-Benzyl-5-carboxy	—	4.03	70JCS(P1)230
5-Carboxy	—	{ 4.27 ^e 9.43	68JCS(C)2076
5-Carboxy-2-methyl	-0.28	3.76	68JCS(C)2076
5-Carboxy-3-methyl	—	4.08	69JCS(C)2379
5-Cyano	—	6.15	73JCS(P1)1629
5-Cyano-2-methyl	-1.35	—	73JCS(P1)1634
5-Formyl-1-methyl ^e	—	—	73JCS(P1)1629
5-Formyl-2-methyl	-0.80	—	73JCS(P1)1629
5-Formyl-3-methyl	-1.54	—	73JCS(P1)1629
5-Hydroxymethyl-3-benzyl	1.15	—	73JCS(P1)1629
5-Hydroxymethyl-2-methyl	1.56	—	73JCS(P1)1629
1-Methyl	2.42	—	73JCS(P1)1629
3-Methyl	2.27	—	69JCS(C)2379
5-Methylamidino [C(=NH)NHMe]	6.35 ^b	12.41 ^c	74JCS(P1)2030
5-Methylamidino-3-benzyl	10.29	—	74JCS(P1)2030
5-Methylamidino-1-methyl	9.26	—	74JCS(P1)2030
5-Methylamidino-2-methyl	10.39	—	74JCS(P1)2030
3-Methyl-5-methylthiomethyleneiminium [C(SMe)= ⁺ NH ₂]	5.47	—	69JCS(C)2379
5-(Methylthio)carbonyl (COSMe)	—	7.12	69JCS(C)2379
Examples where the amino group is not primary			
5-Aminocarbonyl-4-benzylamino	—	7.55	70JCS(C)230
5-Aminocarbonyl-4-methylamino	—	7.96	69JCS(C)152
4-Benzylamino	—	9.66	70JCS(C)230
4-Benzylamino-5-carboxy	—	{ 4.00 9.28	70JCS(C)230

TABLE I (continued)

Substance	pK_a		Reference
	As base	As acid	
5-Cyano-4-dimethylaminomethylenamino ($N=CNMe_2$)			
1-Methyl	3.51 ^f	—	72JCS(P1)461
2-Methyl	3.68	—	72JCS(P1)461
3-Methyl	0.59	—	72JCS(P1)461
4-Diazo	—	-0.4	74TL1609
4-Formamido	—	8.20	68JCS(C)2076

^a 2-Methyl-1,2,3-triazole has no detectable basic properties [59ACS888; 84CHC(5)669].

^b Equilibrium between zwitterion and cation.

^c Equilibrium between zwitterion and anion.

^d Sensitivity to acid prevented determination.

^e That is, 4-amino-1-methyl-1,2,3-triazole-5-carboxaldehyde.

^f Compare dimethylaminomethylenaminobenzene (pK_a 8.71), also its 2-cyano derivative (5.91) [72JCS(P1)461].

^g Dianion.

ionization constants of most of the less complicated 4-amino derivatives of 1,2,3-triazole that have been measured.

The site of protonation in 4-amino-1,2,3-triazole is not the primary amino group, as in **12**, because such a location should move the principal peak of the UV spectrum (239 nm) back to 210 nm, which is the peak of 1,2,3-triazole. (Compare spectra of aniline and its cation; a hypsochromic shift of 26 nm arises upon cation formation) (59MI1). On the contrary, the 239-nm peak of 4-amino-1,2,3-triazole is advanced to 245 nm in the cation (Table II). Hence protonation involves the amidinium-type resonance **13** \leftrightarrow **14**, similar to that responsible for the large increment in basic strength that is effected by inserting an amino group into the 2 or 4 position of pyridine or quinoline (48JCS2240). The increment (pK_2) for 4-amino-1,2,3-triazole is 1.2 (Table I), which is modest, but adequate to support this interpretation. However, although 4-amino-2-methyltriazole is unknown, there is excellent evidence that its 5-substituted derivatives become protonated on the 2-amino group [73JCS(P1)1629]. This occurs because 2-methyltriazole has no detectable basic properties (59ACS888). On the other hand, 4-amino-1- (and 3-)-methyltriazoles are protonated similarly to 4-aminotriazole. It can be seen from Table II that methylation of the 1- or 3-ring-nitrogen atom in 4-amino-1,2,3-triazole affects the base strength very little; benzylation in the 3 position actually decreases it. Insertion of an electron-attracting group into the 5 position of 4-aminotriazole drastically lowers basic strength (e.g., -0.23 for the pK_a of 4-amino-5-aminocarbonyltriazole).

The 5-aminomethyl derivatives of 4-aminotriazole owe their high strength as bases to the aliphatic amino group. The strongest bases in Table II are the 5-methylamidino derivatives **15**, which have pK_a values around 10, except where the presence of a free acidic group (NH) in the nucleus produces zwitterions of which the two pK s are reversed, as in glycine.

The interesting transformation of the 4-amino group to an amidino function (as in the 5-cyano-4-dimethylaminomethylenamino-1,2,3-triazoles **15b**) supplies two examples with evidence of a base-strengthening resonance (see near end of Table I).

Turning to acidic properties, we see that the pK of 1,2,3-triazole (9.4) (a weak acid, very little stronger than phenol) is unchanged by inserting an amino group into the 4 position. However, the acidic strength of 4-aminotriazole is greatly increased by inserting an electron-attracting group into the 5 position, e.g., to pK 7.8 for $CONH_2$, and to 6.2 for CN (see Table I).

1,2,3-Triazole-4-carboxylic acid has pK s of 3.17 and 8.66 [67JCS(B)641] owing to the carboxy and NH groups, respectively. These figures are little affected in 4-amino-5-carboxy-1,2,3-triazole. Conversion of the amino group of 4-aminotriazole to the corresponding diazonium salt increased the acidic strength by nearly 10 units of pK (74TL1609).

C. ULTRAVIOLET SPECTRA

This section begins with the UV spectra of molecules (neutral species). Spectra of the ionized species will be discussed toward the end of the section.

The UV spectrum of the parent (1,2,3-triazole) is almost identical with that of pyrrole, as might be expected from the well-known optically transparent nature of doubly bound nitrogen atoms. In 4-amino-1,2,3-triazole, this characteristic peak is displaced 29 nm to a longer wavelength, without much change in intensity (Table II). Such a displacement resembles the 26-nm shift produced by inserting an NH_2 group into benzene and almost certainly has the same origin.

The expected bathochromic shifts and intensifications of absorbance, which are seen when carbonyl-containing substituents are inserted into the 5 position of 4-aminotriazole, are exemplified by the 5-aminocarbonyl and 5-methoxycarbonyl derivatives, whose main peak is 21 and 22 nm (respectively) more bathochromic than that of the 5-unsubstituted analog, and intensified by $\log \epsilon$ 0.16 and 0.18 (respectively). These changes run parallel to the shift of 45 nm and $\log \epsilon$ 0.17 that occurred when an *o*-carboxy group was introduced into aniline. Such augmentations in 5-membered heterocyclic rings have been compared to spectral results of the resonance delocalization in ethyl

TABLE II
SELECTED UV SPECTRA OF 1,2,3-TRIAZOLES

Substance	Species ^a	Solvent ^b	λ_{\max}^c	log ϵ	Reference
1,2,3-Triazole	A ^d	—	—	—	—
	NS	E	210	3.64	58G977
	C	HCl	211	3.66	58G977
1-Methyl	NS	E	213	3.64	58G977
2-Methyl	NS	7.0	218	3.79	73JCS(P1)1629
4-Amino-1,2,3-triazole (Unsubstituted)	A	12	232	3.62	85MI1
	NS	6.0	240	3.58	85MI1
	C	-1	258	3.20	85MI1
5-Aminocarbonyl (CONH ₂)	A	10.0	223, 265	3.67, 3.90	68JCS(C)344
	NS	4.0	225, 260	3.87, 3.85	68JCS(C)344
	C	-2.4	221, 280	3.91, 3.41	68JCS(C)344
5-Aminocarbonyl-3-benzyl	NS	E	230, 261	3.89, 3.93	56JA5832
5-Aminocarbonyl-3- <i>m</i> -tolyl	NS	M	254	3.99	60CB2001
5-Aminocarbonyl-1-methyl	NS	3.0	273	3.70	68JCS(C)344
5-Aminocarbonyl-2-methyl	NS	7.0	217, 273	3.81, 3.80	68JCS(C)2076
	C	-2.2	224	3.94	68JCS(C)2076
5-Aminocarbonyl-3-methyl	NS	7.0	227, 260	3.99, 3.92	68JCS(C)2076
5-Aminomethyl-3-benzyl	NS	11.0	244	3.70	73JCS(P1)1634
	C	6.0	244	3.70	73JCS(P1)1634
	CC	-2.8	266	3.65	73JCS(P1)1634
5-Aminomethyl-1-methyl	NS	10.0	249	3.62	73JCS(P1)1634
	C	4.0	249	3.56	73JCS(P1)1634
	CC	-1.2	266	3.46	73JCS(P1)1634
5-Aminothiocabonyl	NS	E	$\left\{ \begin{matrix} 272, 311, \\ 321 \end{matrix} \right.$	$\left\{ \begin{matrix} 3.87, 4.00 \\ 3.94 \end{matrix} \right.$	56JA5832
3-Benzyl	NS	7.0	241	3.73	70JCS(C)230
	C	-0.3	262	3.66	70JCS(C)230

(continued)

TABLE II (continued)

Substance	Species ^a	Solvent ^b	λ_{\max}^c	log ϵ	Reference
3-Benzyl-5-carboxy	A	7.9	225, 254	3.89, 3.87	70JCS(C)230
	NS	2.0	229, 261	3.86, 3.93	70JCS(C)230
3-Benzyl-5-cyano	NS	E	228, 251	3.95, 3.82	70JCS(C)230
3-Benzyl-5-ethoxycarbonyl	NS	E	231, 262	3.83, 3.91	56JA5832
5-Carboxy	A	7.0	217, 256	3.75, 3.75	68JCS(C)2076
	NS	2.0	226, 261	3.85, 3.86	68JCS(C)2076
5-Carboxy-2-methyl	A	7.0	266	3.80	68JCS(C)2076
	NS	1.8	276	3.78	68JCS(C)2076
	C	-2.4	227	3.88	68JCS(C)2076
5-Cyano	A	9.0	252	3.74	73JCS(P1)1629
	NS	3.0	251	3.77	73JCS(P1)1629
5-Cyano-1-methyl	NS	E	215, 283	3.76, 3.74	73JCS(P1)1634
5-Cyano-2-methyl	NS	7.0	216, 269	3.74, 3.73	73JCS(P1)1634
5-Cyano-3-methyl	NS	M	225, 251	3.95, 3.78	69JCS(C)2379
5-Formyl-1-methyl ^e	NS	3.0	243, 316	3.64, 3.83	73JCS(P1)1629
5-Formyl-2-methyl	NS	2.0	236, 302	3.60, 3.79	73JCS(P1)1629
	C	-4	241	3.90	73JCS(P1)1629
5-Formyl-3-methyl	NS	2.0	237, 287	3.60, 3.96	73JCS(P1)1629
	C	-4	241, 301	3.67, 3.91	73JCS(P1)1629
5-Methoxycarbonyl	NS	6.0	226, 261	3.87, 3.90	68JCS(C)2076
5-Hydrazinocarbonyl	NS	E	227, 262	3.89, 3.83	56JA5832
5-Hydroxymethyl-2-methyl	NS	4.0	252	3.76	73JCS(P1)1629
	C	-2	220	3.81	73JCS(P1)1629
1-Methyl	NS	5.0	241	3.49	73JCS(P1)1629
	C	0	262	3.17	73JCS(P1)1629
3-Methyl	NS	7.0	238	3.73	69JCS(C)2379
	C	-0.2	259	3.63	69JCS(C)2379
5-Methylamidino-1-methyl ^f	NS	11.8	258	3.69	74JCS(P1)2030
	C	7.0	283	3.64	74JCS(P1)2030

5-(Methylthio)carbonyl (COSMe)	NS	5.0	237, 293	3.75, 4.06	69JCS(C)2379
Examples where the amino group is not primary					
5-Aminocarbonyl-4-benzylamino	A	10.0	229, 276	3.78, 3.80	70JCS(C)230
	NS	5.0	233, 272	3.93, 3.80	70JCS(C)230
5-Aminocarbonyl-4-methylamino	NS	5.0	232, 275	3.93, 3.86	69JCS(C)152
5-Aminocarbonyl-4- <i>m</i> -toluidino	NS	M	264	4.24	60CB2001
4-Anilino	NS	E	251	4.20	58SA250
4-Benzylamino	NS	M	253	3.63	70JCS(C1)230
4-Benzylamino-5-carboxy	AA	12.0	227, 263	4.11, 4.12	70JCS(C1)230
	A	6.6	230, 266	3.85, 3.71	70JCS(C1)230
	NS	2.0	233, 272	4.00, 3.87	70JCS(C1)230
5-Cyano-4-dimethylaminomethylenamino (N=CHNMe ₂)					
1-Methyl	NS	7.0	281	4.17	72JCS(P1)461
	C	1.0	253	4.21	72JCS(P1)461
2-Methyl	NS	7.0	266	4.26	72JCS(P1)461
	C	1.0	244	4.27	72JCS(P1)461
3-Methyl	NS	7.0	267	4.14	72JCS(P1)461
	C	-1.6	235	4.07	72JCS(P1)461
5-Cyano-4-ethoxymethyleneamino (N=CHOEt)					
1-Methyl	NS	C	255	4.04	73JCS(P1)2659
2-Methyl	NS	C	247	4.07	73JCS(P1)2659
4-Formamido	A	11.0	232	3.94	68JCS(C)2076
	NS	6.0	224	3.96	68JCS(C)2076

^a A, anion; C, cation; NS, neutral species (molecule); AA, dianion.

^b The solvents: Numerals (e.g. 6.0) indicate the pH of an aqueous buffer, chosen (from pK values) so that only one ionic species is present. Other solvents: C, cyclohexane; E, ethanol; HCl, dilute hydrochloric acid; M, methanol; and NaOH, dilute sodium hydroxide.

^c Shoulders are in italics.

^d No spectrum of the anion could be found in literature.

^e For pKs and spectra of 4-formyl-1,2,3-triazole, see Ref. 67JCS(B)641.

^f UV spectra of several related amidines are in same reference.

β -aminocrotonate, as supported by such canonical forms as $\text{MeC}(=\text{NH}_2)\text{-C}=\text{C}(\text{O}^-)\text{OEt}$ (71T5873). The 260–270-nm peak in the UV spectra of 5-carbonyl-substituted 4-amino-1,2,3-triazoles is accompanied by another peak near 220 nm, which arises from transitions across the triazole ring.

The insertion of a methyl or a benzyl group into the 3 position of 4-amino-5-aminocarbonyl-1,2,3-triazole affects the spectrum very little, and a phenyl group is even slightly hypsochromic (see 4-amino-5-aminocarbonyl-3-*m*-tolyl-1,2,3-triazole in Table II). On the other hand, insertion of a methyl group into the 1 or 2 position has a significant bathochromic effect, which operates even more strongly in the corresponding aldehydes (4-amino-5-formyl-*x*-methyltriazoles); the cyano analogs behave similarly (see Table II). These shifts can have diagnostic value in locating the position of alkylation.

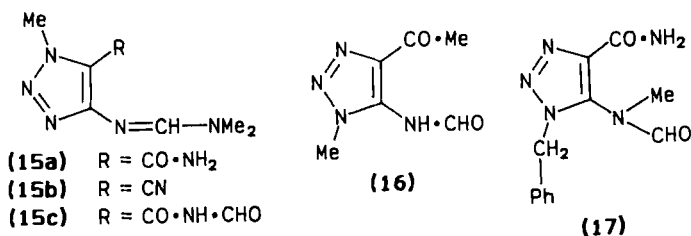
Ultraviolet spectra have proved useful in following Dimroth rearrangements (Section III,D) where a 3-alkyl (or 3-aryl) group becomes a 4-alkylamino (or 4-arylamino) group. Four such pairs can be seen in Table II, e.g., 4-amino-3-benzyl- and 4-benzylamino-1,2,3-triazoles. In each case, a bathochromic shift of about 10 nm occurs. $^1\text{H-NMR}$ spectra are also useful in following such reactions (see Section II,D).

The UV spectra of the following are available: 4-arylsulfonamido-1,2,3-triazoles and their N-methylated derivatives (75G583); 5-aminocarbonyl- and 5-formylaminocarbonyl-4-dimethylaminomethylenamino-1- (also 2-)-1,2,3-triazole [72JCS(P1)461]; 4-amino- and 4,4-diaminomethylenamino-5-(2,2-dicyanovinyl)-1,2,3-triazoles, and their 2-cyano-2-ethoxycarbonylvinyl analogs; 5-(2-cyano-) (also 2,2-dicyanovinyl)-4-ureido- and 4-thioureido-1,2,3-triazoles [73JCS(P1)1620]; 4-amino-1,2,3-triazole-5-carboxamidine and -5-carboxamidoxime (60JA3189); and the azines, oximes, hydrazones of 5-formyl-1,2,3-triazoles that are further substituted in the 4 position by amino, ureido, thioureido, diaminomethylenamino, hydroxyiminomethylenamino, or hydrazonomethylenamino groups [73JCS(P1)1625].

Ionized species. The 4-aminopyridinium-type of resonance, which underlies the bathochromic shift that occurs when 4-amino-1,2,3-triazole is converted to the cation, was discussed in Section II,B. A similar shift is seen in all 1- and 3-alkylated derivatives, whereas all of the 2-methyl derivatives lose their long-wave peak when converted to the cation (see the four examples in Table II). This loss signifies protonation on the 4-amino group, as in aniline [73JCS(P1)1629]. This divergence occurs because the rules of valence do not allow 2-methyl-1,2,3-triazole to exert the base-strengthening resonance that is characteristic of unsubstituted 1,2,3-triazole [84CHC(5)669, p. 690] and is exerted by the 1- and 3-alkyl derivatives. These observations can help assign the position of a group acquired in an alkylation reaction.

In 4-amino-5-aminomethyl-1,2,3-triazoles, the first proton is captured by the more basic aliphatic amino group, so that the spectrum does not change

until the dication is formed at a lower pH. The anionic spectrum of 1,2,3-triazole is unknown. Conversion of 4-amino-1,2,3-triazole to the anion produces a hypsochromic shift, whereas there is little change on converting 4-amino-5-cyano-1,2,3-triazole to its anion, and a bathochromic shift takes place for the 5-aminocarbonyl analog. Thus these three available examples provide no evident regularity. Comparison of the pKs and spectra of 1,2,3-triazole-5-carboxylic acid [67JCS(B)641] with those of the three carboxylic acids in Table II provides no evidence of zwitterion formation.



D. NMR SPECTRA

¹H-NMR spectra are much used for characterizing substituted 4-amino-1,2,3-triazoles. Table III contains sufficient examples to illustrate the range of chemical shifts exhibited by the commoner substituents. In this table, their movement to lower field, in response to the deshielding effect of electron-attracting groups, can be followed. Signals for NH, although broad, as would be expected, are usually sharp enough in this series to be easily measured, whether cyclic or exocyclic. However, their chemical shift is highly variable. Complex spin systems are rarely encountered in the aminotriazoles; most of the examples of spin-spin coupling were quickly resolved by deuteration, as exemplified in Table III.

A most unusual ¹H-NMR spectrum was given by 3-benzyl-4-*N*-methylformamido-1,2,3-triazole-5-carboxamide (17), which furnished doublet signals for each of four substituents (CHO, NH, CH₂, and CH₃), which coalesced to four singlets at 90°C. This reversible twinning (see Fig. 1) was attributed to rotational isomerism arising from double-bond character in the link between the ring and the exocyclic nitrogen atom, and a heightened energy barrier to coalescence. This and two other examples are described in Ref. [81JCS(P1)2344].

The nature of the solvent exerts only a moderate influence on the position of signals in this series. For example, 4-amino-5-hydroxymethyl-2-methyl-1,2,3-triazole gave a 2-Me signal at δ 3.91 in perdeuterated dimethyl sulfoxide, at

TABLE III
SELECTED ¹H-NMR VALUES (δ)^a

Substance	Signals	Reference
1,2,3-Triazole	7.91 (H-4), 7.91 (H-5), 13.50 (NH)	73NMR219
1-Methyl	4.09 (3H, Me), 7.72 (H-4), 8.08 (H-5)	73NMR219
2-Methyl	4.17 (3H, Me), 7.77 (H-4), 7.77 (H-5)	73NMR219
4-Amino-1,2,3-triazole	4.97*br (2H, NH ₂), 6.33*br (3-NH), 7.03 (H-5)	71JHC51
5-Acetamidomethyl-1-methyl	1.82 (3H, Ac), 3.84 (3H, 1-Me), 4.24 [†] (2H, d, J 6 Hz; 5-CH ₂ coupled to NHCO), 4.63*br (2H, 4-NH ₂), 8.3 br (CONH)	73JCS(P1)1634
5-Aminocarbonyl-3-methyl	3.76 (3H, Me), 7.05*br, (NH), 7.34*br (NH)	81JCS(P1)2344
5-Aminomethyl-1-methyl ^b	1.8*br (2H, CH ₂ NH ₂), 3.64 (2H, CH ₂), 3.81 (3H, Me), 4.50 br (2H, 4-NH ₂)	73JCS(P1)1634
3-Benzyl	5.40 (2H, CH ₂), 5.61* (2H, NH ₂), 6.88, (H-5), 7.34 (5H, Ph)	70JCS(C)230
3-Benzyl-5-carboxy	5.46 (2H, CH ₂), 6.57* (2H, NH ₂), 7.30 (5H, Ph)	70JCS(C)230
3-Benzyl-5-formyl	5.46 (2H, CH ₂ Ph), 7.15*br (2H, NH ₂), 7.32 (5H, Ph), 9.90 (CHO)	73JCS(P1)1629
3-Benzyl-5-hydroxymethyl	4.42 [†] (2H, d, J 6 Hz, CH ₂ O), 4.73* (t, J 6 Hz, OH), 5.34 (2H, CH ₂ Ph), 5.42* (2H, NH ₂), 7.30 (5H, Ph)	73JCS(P1)1629
5-Carboxy-1-methyl	4.15 (3H, Me), 7.93*br (2H, NH ₂)	72JCS(P1)449
5-Cyano-1-methyl	4.06 (3H, Me), 6.31* (2H, NH ₂)	73JCS(P1)1634
5-Ethoxalylaminomethyl-1-methyl ^b	1.26 (3H, t, CH ₂ CH ₃), 3.86 (3H, 1-Me), 4.25 (4H, m, CH ₂ NH + CH ₂ Me), 4.67*br (2H, NH ₂), 9.35*br (NH)	81JCS(P1)887
5-Ethoxycarbonylaminomethyl-1-methyl ^b	1.16 (3H, t, J 7 Hz, Me of Et), 3.87 (3H, 1-Me; obscures q of Et), 4.04 [†] (2H, d, 5-CH ₂ coupled to NHCO), 7.5*br (CONH)	81JCS(P1)887
5-Formyl-1-methyl	4.11 (3H, Me), 6.30*br (2H, NH ₂), 9.90 (CHO)	73JCS(P1)1629
5-Hydroxymethyl-2-methyl	3.91 (3H, Me), 4.45 [†] (2H, d, J 6 Hz, CH ₂), 4.89* (2H, NH ₂), 4.99* (t, J 6 Hz, OH)	73JCS(P1)1629
5-Methoxycarbonyl-2-methyl	4.00 (3H, OMe), 4.13 (3H, NMe), 4.90* (2H, NH ₂)	73JCS(P1)1629
5-Methoxycarbonyl-3-phenyl	4.00 (3H, OMe), 7.55 (5H, Ph)	71JCS(C)706
1-Methyl	3.87 (3H, Me), 4.63*br (2H, NH ₂), 7.09 (CH)	73JCS(P1)1629
3-Methyl	3.71 (3H, Me), 5.40*br (2H, NH ₂), 6.78 (CH)	73JCS(P1)1629
1-Methyl-5-methylamidino ^b	2.81 (3H, 5-Me), 4.00 (3H, 2-Me), 4.97 (2H, 4-NH ₂), 6.3*br (C=NH)	74JCS(P1)2030

1-Methyl-5-oxamoylaminomethyl ^b	3.91 (3H, Me), 4.24 [†] (2H, d, \underline{J} 6 Hz, CH ₂), 7.94*(NH), 9.3*br (NH)	81JCS(P1)887
Non-primary amines		
4-Acetamido-5-aminocarbonyl	2.16 (3H, Me), 7.51*br (NH), 7.82 br (NH)	73JCS(P1)943
4-Acetamido-5-cyano-1-methyl	2.17 (3H, COMe), 4.88 (3H, 1-Me), 11.4*br (NH)	73JCS(P1)2659
5-Acetyl-4-formamido-3-methyl (16)	2.56 (3H, COMe), 3.90 (3H, 3Me), 8.34 (CHO)	77JCS(P1)1819
5-Aminocarbonyl-2-benzyl-4-formamido	5.62 (2H, CH ₂), 7.18 (5H, Ph), 7.68*br (2H, NH ₂) 8.65*(CHO), 9.84*br (NH)	72JCS(P1)468
5-Aminocarbonyl-4-methylamino	2.81 [†] (3H, d, \underline{J} 6 Hz, Me), 5.9*br (4-NHMe), 7.0*br (NH), 7.2*br (NH)	81JCS(P1)2344
3-Benzyl-4-diacetylamino ^c	2.00 (6H, 2 × Me), 5.32 (2H, CH ₂), 7.29 (5H, Ph), 7.56 (H-5)	78JCS(P1)427
4-Benzylamino	4.35 [†] (2H, d, CH ₂ coupled to NH), 6.05* (3-NH), 7.05 (H-5), 7.35 [†] (6H, Ph + 4-NH)	70JCS(C)230
4-Benzylamino-5-carboxy	4.45 (2H, CH ₂), 6.4*br (3-NH), 7.33 (5H, Ph)	70JCS(C)230
5-Cyano-4-ethoxymethylen- amino-1-methyl ^b	1.38 (3H, t, \underline{J} 7 Hz, CH ₂ CH ₃), 4.19 (3H, 1-Me), 4.39 (2H, q, \underline{J} 7 Hz, CH ₂ CH ₃), 8.63 (1H, N=CH)	73JCS(P1)2659
4-Dimethylaminomethylenamino-1-methyl 5-Aminocarbonyl (15a) ^d	3.12 + 3.19 (each 3H, NMe ₂), 4.36 (3H, 1-Me), 6.1*br (2H, NH ₂), 8.69 (N=CHNMe ₂)	72JCS(P1)461
5-Cyano (15b) ^d	3.07 (6H, NMe ₂), 4.11 (3H, 1-Me), 8.43 (N=CHNMe ₂)	72JCS(P1)461
5-Formamidocarbonyl (15c) ^d	3.12 + 3.17 (each 3H, NMe ₂), 4.29 (3H, 1-Me), 8.64 (1H, N=CHNMe ₂), 9.48 [†] , d, \underline{J} 11 Hz (CHO coupled to NH), 11.7*br (NH)	72JCS(P1)461
4-Ethoxycarbonylamino- 5-formyl-1-methyl ^b	1.41 (t, Me of Et), 4.46 (q, CH ₂), 8.65 (CHOEt)	73JCS(P1)2037
4-Formamido-1-methyl	4.10 (3H, Me), 7.07 (H-5), 8.31 [†] (d, CHO coupled to NH)	78JCS(P1)427

*Signal disappeared on deuteration.

[†]Doublet collapsed to singlet on deuteration.

^cWhen solvent is not otherwise specified, perdeuterated DMSO was used with tetramethylsilane as internal standard. Signals are 1H and s, except where otherwise marked.

^bSeveral related compounds are in same reference.

^cD₂O also present.

^dIn CDCl₃.

^eThis signal was not visible below 40°C.

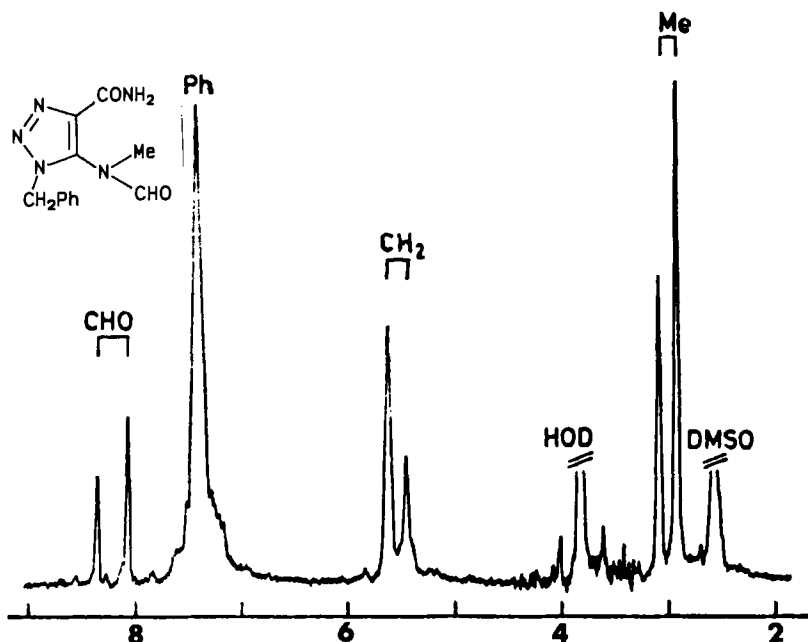


FIG. 1. ¹H-NMR spectrum (δ) of 3-benzyl-4-N-methylformamido-1,2,3-triazole-5-carboxamide (17) in (CD₃)₂SO + D₂O at 27°C and 100 MHz.

4.00 in deuterium oxide, at 4.22 in 10 *N* deuterochloric acid, and at 3.90 in anhydrous trifluoroacetic acid [73JCS(P1)1629].

¹H-NMR spectra have greatly assisted in following the course of rearrangements, also in monitoring the purity of the products from these, and in reporting any retrogression (to starting material) caused by heat or storage. In the Dimroth rearrangement (Section III,D) of 4-amino-3-benzyltriazoles to 4-benzylaminotriazoles, the signal of the methylene portion of the benzyl group is advanced about 1.2 ppm upfield [70JCS(C)230] and the corresponding figure for a methyl group averages 1.0 ppm [81JCS(P1)2344]. These large shifts have proved useful diagnostically. Two such pairs of Dimroth isomers can be compared in Table III. Similar monitoring proved useful in Dimroth rearrangements of 4-amino-5-aminocarbonyl-3-aryl-1,2,3-triazoles (80FES298). Some 4-amino-5-(methylthio)carbonyl-1,2,3-triazoles, such as 18, were distinguished from the isomeric 4-amino-5-methoxy(thiocarbonyl)-triazoles by the characteristic MeS signal at δ 2.32, whereas MeO would register about 4.0 [69JCS(C)2379].

¹H NMR was used to study the equilibrium between 3-benzenesulfonyl-4-diethylamino-1,2,3-triazoles and the open-chain diazoarylsulfonamidines

with which they are in equilibrium (for chemistry, see p. 144) (70JOC3444). ^1H NMR has helped to assign the site of glycosidation in triazole 1-, 2-, and 3-nucleosides (70JHC1269; 72JHC1195).

Configurational assignments were made with the help of NMR for pairs of isomers of 3-aryl-4-diethylamino-2-ethyl-5-methyl-3,4-dihydrotriazoles. Those whose signal appeared at a lower field were classified as *trans*; the difference between the *cis* and *trans* signals averaged 0.33 ppm (in CDCl_3) [72JCS(P1)997]. The conformations of the 4-amino analogs were also investigated [72OMR247; 74ACS(B)425]. NMR data are recorded for several related triazolines [67G579; 72JCS(P1)769].

Other areas where ^1H -NMR spectra have helped assign or confirm structures of 1,2,3-triazoles include: acyl derivatives of 4-aminotriazole-5-carboxamide, including examples that are acylated on a ring-nitrogen atom, or on the amide group, or on the 4-amino group, as well as in di- and even tri-acetylated examples [71JCS(C)706]; 4-arylsulfonamidotriazoles and their N-methylated or N-acetylated products (75G583; 76G1); of 4,5-diaminotriazoles (72JOC4124); of 5-cyano- and 5-carboxy-4-tosylaminotriazoles (75LA2159); of 4-amino- and 4,4-diamino-methylenamino-5-(2,2-dicyanovinyl)triazoles and their 2-cyano-2-ethoxycarbonylvinyl analogs [73JCS(P1)1620]; of 5-(2-cyano-, and 2,2-dicyano)vinyl-4-ureido-(and 4-thioureido)triazoles [73JCS(P1)1620]; of the azines, oximes, and hydrazones of 5-formyltriazoles that are further substituted in the 4 position by one of the following groups: amino, ureido, thioureido, diaminomethyleneamino, hydroximinomethyleneamino, or hydrazonomethyleneamino [73JCS(P1)1625]. Only one example (^{13}C) [85MRC(23)842] was found of studies on 4-aminotriazoles with nuclei other than the proton. ^{13}C -NMR data are available for 1,2,3-nonaminated 1,2,3-triazoles [84CHC(5)669; 78LA1241; 74JOC357].

E. INFRARED SPECTRA

The strong NH-stretching band of 1,2,3-triazole occurs at 3522 cm^{-1} in the vapor phase and at 3470 cm^{-1} in carbon tetrachloride solution [69JCS(B)307]. However, 4-amino-1,2,3-triazoles have usually been examined in the solid state for which KBr discs and nujol mulls gave similar results. A comparison of the spectra of one example, 4-amino-5-ethoxycarbonyl-3-phenyl-1,2,3-triazole, in chloroform and in a KBr disc, showed a slightly higher frequency of the NH-stretching bands in the former (71T5873).

Nuclear NH stretching bands are not easily distinguished from those due to a primary amino group, as can be seen by comparing the high frequency bands of 4-amino-5-cyanotriazole (3450 , 3400 , 3320 , and 3250 cm^{-1})

[73JCS(P1)1629] with those of its 1-methyl derivative (3420, 3330, and 3200 cm^{-1}) [73JCS(P1)1634]. In these compounds, and in the isomeric 2- and 3-methyl derivatives [69JCS(C)2379], a sharp CN-stretching band appears in the 2210–2240- cm^{-1} range. A sharp and prominent band between 1640 and 1660 cm^{-1} was attributed to NH_2 bending, and another prominent band between 1567 and 1600 cm^{-1} was assigned to vibration of the whole triazole ring (75BSF1219).

Typical of the 4-amino-5-aminocarbonyltriazoles, much used as intermediates, 4-amino-1,2,3-triazole-5-carboxamide presents an intense, rather broad band centered at 1675 cm^{-1} and also a strong peak at 1610 cm^{-1} , attributed, respectively, to Nakanishi's "Amide I (CO stretching)" and "Amide II (NH bending mixed with some CN stretching)" (B62MI1). The 1-methyl derivative shows these bands at 1660 and 1600 and the 2-methyl derivative at 1655 and 1610 cm^{-1} [69JCS(C)2379]. In spectra of the related secondary amides, these bands are relegated to lower frequencies and a third, related band can often be seen at about 1300 cm^{-1} [69JCS(C)2379].

A table of carbonyl-stretching frequencies is available for 4-amino-1,2,3-triazole-5-carboxamide (and derivatives) variously acetylated on a ring-nitrogen atom, on the 4-amino group, or on the amide group [71JCS(C)706].

The CO-stretching frequencies (in cm^{-1}) of a typical ester, ketone, and aldehyde are, respectively, exemplified by 4-amino-5-methoxycarbonyl-2-methyl- {1700s and 1145s [73JCS(P1)1629]}, 5-acetyl-4-amino-3-methyl- {1638s [77JCS(P1)1819]}, and 4-amino-5-formyl-3-methyl- {1650s [73JCS(P1)1629]} triazoles. From analogy with ethyl β -aminocrotonate, two further bands (1615s and 1555m) in the esters were assigned to a coupled group frequency swinging of $\text{C}=\text{O}$, $\text{C}=\text{C}$, CN, and NH_2 bonds (71T5873). 4-Amino-5-carboxy-1-methyl-1,2,3-triazole absorbs most strongly at 1695 cm^{-1} , characteristic of the dimer of an aromatic carboxylic acid, and other strong bands are at 1630, 1320, 1180, and 775 cm^{-1} [69JCS(C)2379].

Some interesting anomalies should be noted. The strong absorption at 1725 cm^{-1} in **15c** (due to the formyl group, CO stretching), which appeared in the spectrum of a chloroform solution, was much attenuated in the solid state (see Fig. 2) [72JCS(P1)461]. In 5-acetamidomethyl-4-amino-1,2,3-triazoles, the CO-stretching frequency tends to be low, strikingly so in 5-acetamidomethyl-4-amino-2-methyl-1,2,3-triazole (1625 cm^{-1}). This effect was traced to internal hydrogen bonding [73JCS(P1)1634].

Some other characteristic group absorptions will now be summarized. The thiolester group in 4-amino-3-methyl-5-(methylthio)carbonyl-1,2,3-triazole (the 3-Me derivative of **18a**) displayed two strong bands of equal intensity: 1630 ($\text{C}=\text{O}$ stretching) and 900 ($\text{C}-\text{S}$ stretching) cm^{-1} . This and related examples are discussed in Refs. 69JCS(C)2379 and 72JCS(P1)461. The

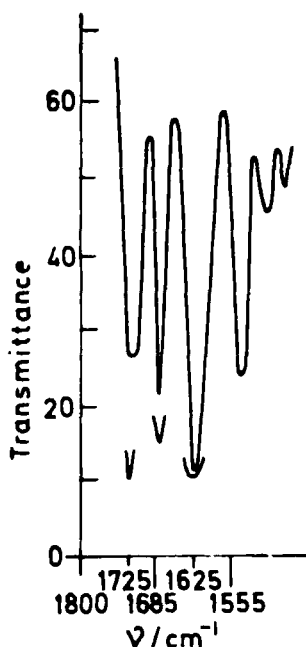


FIG. 2. Solid-state IR spectrum of 4-dimethylaminomethylenamino-1-methyl-5-*N*-formyl-carboxamide (**15c**) in nujol (the continuous curve), and in chloroform (1% solution in a 0.5-cm cell) (shown as tips of the three main peaks).

methoxy (thiocarbonyl) isomers would be expected to absorb very differently, namely, at about 1100 cm^{-1} ($\text{C}=\text{S}$ stretching).

Highly characteristic bands in amidines, such as 4-amino-1-methyl-1,2,3-triazole-5-carboxamidine, were assigned to the NH stretch ($3200\text{--}3480$), the CN stretch ($1610\text{--}1660$), and the NH bend ($1520\text{--}1610 \text{ cm}^{-1}$) [74JCS(P1)2030]. In spectra of a series of 4-amino-5-aminomethyltriazoles, the in-plane NH bending was strongly expressed in the $1540\text{--}1590 \text{ cm}^{-1}$, and the NH stretching in the $3250\text{--}3400 \text{ cm}^{-1}$ area [73JCS(P1)1634]. For some guanidino derivatives of 1,2,3-triazoles, see Refs. 75JCS(P1)345 and 80JCS(P1)2918.

Spectra of 4-dimethylaminomethylenamino- [72JCS(P1)461] and 4-ethoxymethylenaminotriazoles [73JCS(P1)2659] showed strong $\text{C}=\text{N}$ stretching around 1635 cm^{-1} . For derivatives of 4-aminotriazole-5-aldehyde, see Ref. 73JCS(P1)2037 (acetal), and Ref. 73JCS(P1)1629 (azine, phenylhydrazone, and phenylsemicarbazone). Infrared spectra are recorded for 4-arylsulfonamidotriazoles and their *N*-methylated and -acetylated products (SO_2 stretch,

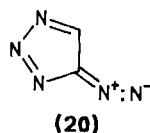
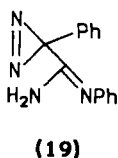
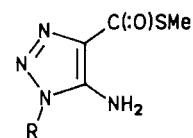
1158 and 1356 cm^{-1}) (75G583), for derivatives of 4,5-diaminotriazole (72JOC4124), and for 1,2,3-triazole *N*-oxides [66JCS(B)1243].

F. MASS SPECTRA

Upon electron impact, the molecular ion (M^+) of 1,2,3-triazole loses one molecule of nitrogen followed by one of hydrocyanic acid; some substituents can reverse this order or even become degraded first [730MS271; 79JCS(P1)15; 84CHC(5)669]. The mass spectrometry of 4-amino-1,2,3-triazoles follows similar lines with some interesting exceptions. 3-Benzyl-4-*N*-methylformamido-1,2,3-triazole-5-carboxamide (**17**) eliminated a mass of 28 from M^+ , which was shown by precision spectrometry to be CO and not the expected NN; this somewhat surprising event also occurred with the isomeric 3-benzyl-4-methylamino-1,2,3-triazole-5-*N*-formylcarboxamide [81JCS(P1)2344]. The elements of carbon monoxide were split out also when the usual electron-impact spectrum was attempted for 3-benzyl-4-formamido-1,2,3-triazole-5-(*N*-methylcarboxamide), which registered only 231 for M^+ ; however, the correct molecular ion (259) was obtained by the chemical ionization modification [78JCS(P1)513]. In these studies, the benzyl radical unflinchingly registered a strong signal at 91 *m/e*. Other applications of mass spectrometry include studies of 4-amino-3-cyclohexyltriazole [71JCS(C)1501], 3-phenyl-4-vinylaminotriazoles [73JCS(P1)943], and 4-arylsulfonamidotriazoles and their *N*-methyl and *N*-acetyl derivatives (75G583).

G. PHOTOLYSIS AND THERMOLYSIS

Irradiation of 4-amino-3,5-diphenyl-1,2,3-triazole, in ethanol with a high-pressure mercury lamp for 40 hr, gave an equilibrium mixture of starting material and the Dimroth-rearrangement product, 4-anilino-5-phenyl-1,2,3-triazole (35% yield), separated by thin-layer chromatography. When the product was similarly irradiated, the equilibrium was reestablished (see also



Section III,C). The authors prefer a diazirine structure (19) to Dimroth's postulated diazo intermediate (77BCJ2505).

Gas-phase pyrolysis of 1,2,3-triazole produced vinyl azide and its decomposition products (83JA7681). 4-Diazo-1,2,3-triazole (20) (prepared by diazotizing 4-aminotriazole in water), when refluxed in benzene, gave 4-phenyl-1,2,3-triazole (53% yield) and a mixture of cyanobicycloheptatrienes (15%). Photolysis proceeded similarly, except that the latter products preponderated (82TL5115).

III. Reactivity

Usually it is convenient to discuss reactivity in a heterocyclic series under two headings: "Reactivity at the Ring Atom," followed by "Reactivity of the Substituents." This treatment does not suit the 4-amino-1,2,3-triazoles because the frequently used alkylating agents can attack either a ring-nitrogen atom or the exocyclic amino group (or both!). Hence it seemed best to present in one place what is known of the rules that favor one process over the other, so that either may be implemented at will. Relevant, too, is the Dimroth rearrangement and its retrogression (Section III,D), which enable an alkyl group to be shuttled between N-3 and the primary amino group.

In what follows, reaction details will be abbreviated as in the following example: (90°C, 1 hr, 85%) means that the reactants were heated at 90°C for one hour, and furnished an 85% yield.

A. ACYLATIONS, ALKYLATIONS, AND THEIR REVERSAL

The insertion of alkyl and acyl groups (and their removal) constitute about half of all reactions to which 4-amino-1,2,3-triazoles have been subjected. Acylation (particularly formylation and trifluoroacetylation) have proved very useful for facilitating monomethylation of the 4-amino group.

1. *N*-Acylation and Deacylation

The weak nucleophilicity of the 4-amino group, even when further depleted by an electron-attracting group in the 5 position, does not usually prevent acylation of the exocyclic group taking precedence over that of a ring-NH group. When, in addition, strong hydrogen bonding is present (met principally in the 4-amino-5-formyltriazoles), the 4-amino group cannot be acylated [73JCP(P1)2037].

For formylation, the most used methods are (1) refluxing with anhydrous formic acid; (2) at last, but acetic anhydride is also present; and (3) stirring with cold, freshly prepared (70OS1) acetic formic anhydride. Procedures (2) and (3), which are more vigorous than (1), appear to be equally effective, but (3) is preferred for heat-sensitive material. Some examples follow. 4-Aminotriazole hydrochloride, refluxed with formic acid, gave 4-formamidotriazole (1 hr, 75%) [68JCS(C)2076]. 4-Methylaminotriazole-5-carboxamide, heated with formic acid and acetic anhydride, yielded 4-*N*-methylformamidotriazole-5-carboxamide (100°C, 1 hr, 90%); 3-benzyl-4-methylaminotriazole-5-carboxamide reacted similarly [81JCS(P1)2344]. 4-Amino-3-benzyl-5-cyanotriazole, stirred with freshly prepared acetic formic anhydride, gave 3-benzyl-5-cyano-4-formamidotriazole (22°C, 17 hr, 91%) [75JCS(P1)345]. The 1- and 2-methyl analogs were prepared similarly [73JCS(P1)2659].

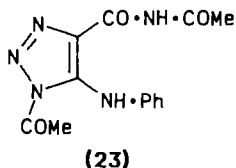
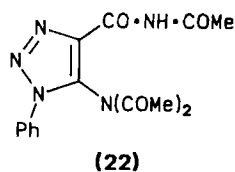
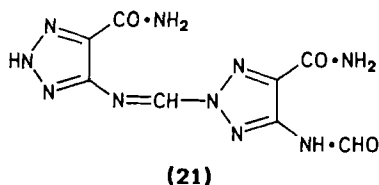
Whereas 4-amino-3-methyltriazole-5-carboxamide, stirred with acetic formic anhydride, gave the 4-monoformylated derivative (24°C, 40 hr, 97%) [68JCS(C)2076], 4-amino-3-benzyltriazole-5-carboxamide, under these conditions, produced the 4-diformylated product (95%). When the latter was refluxed with methanol, the monoformylated analog was obtained (50 min, 95%) [69JCS(C)152].

It is unusual for a Dimroth rearrangement (defined in Section III,D) to occur during formylation, but the following example is cautionary. 5-Aminomethyl-3-benzyl-4-methylaminotriazole and acetic formic anhydride, stirred in pyridine, gave 4-benzylamino-5-formamidomethyl-3-methyltriazole (23°C, 15 hr, 84%). Most likely, the use of pyridine determined this outcome [81JCS(P1)2344].

Formylation can be directed to a 5-aminocarbonyl group, if so desired. 3-Benzyl-4-methylaminotriazole-5-carboxamide, heated with dimethylformamide and phosphoryl chloride, furnished 3-benzyl-4-methylaminotriazole-5-*N*-formylcarboxamide (100°C, 15 min, 50%) [81JCS(P1)2344].

An unusual, and outstandingly useful, product from formylating a simple triazole is the anhydrodimer, produced by refluxing 4-aminotriazole-5-carboxamide with formic acid (30 min, 98%). The same substance was obtained with acetic formic anhydride (25°C, 20 hr, 95%). The product, $C_8H_8N_{10}O_3$, assigned structure **21**, gave an excellent yield of 2-benzyl- and 2-methyl-4-formamidotriazole-5-carboxamide when gently alkylated (see Section III,A,2,b). No other approach is so convenient for entering the 2-methyl- and 2-benzyltriazole series. Curiously, no other anhydrodimer has been reported.

Deformylation is readily brought about with alkali. 4-Formamido-2-methyltriazole-5-carboxamide, set aside in *N*-sodium hydroxide, gave the 4-amino analog (24°C, 20 hr, 90%) [68JCS(C)2076]. 3-Benzyl-5-cyano-4-



N-methylformamidotriazole was deformylated by a brief refluxing with 1.5 *N* ethanolic sodium hydroxide (5 min, 95%) [81JCS(P1)2344].

An unexpected acetylation troubled two laboratories where 4-amino-1,2,3-triazole-5-carboxamide, while being recrystallized from anhydrous acetic acid, deposited a crop that was reported as a diacetyl derivative [57JOC707; 71JCS(C)2156]. However, this product, of which a 64% yield was obtained by 5 hr refluxing, turned out to be a 1:1-lattice complex of 4-acetamidotriazole-5-carboxamide with acetic acid [73JCS(P1)943]. No similar example has been reported.

Acetic anhydride has proved the most useful acetylating agent in this series, and some examples of its use follow. 1-Benzyl-4,5-diaminotriazole, set aside in this anhydride, produced 4,5-diacetamido-1-benzyltriazole (25°C, 15 hr, 45%), but decreasing the reaction time to 10 min gave 4-acetamido-5-amino-1-benzyltriazole (53%) (72JOC4124). When 4-amino-5-cyano-1-methyltriazole and acetic anhydride were stirred in pyridine (23°C, 15 hr), and the product refluxed with ethanol (1 hr), 4-acetamido-5-cyano-1-methyltriazole (93%) was obtained [73JCS(P1)2659]. Severer conditions were required by 4-amino-3-benzyl-5-cyanotriazole, namely, refluxing with acetic anhydride and pyridine, which furnished 4-acetamido-3-benzyl-5-cyanotriazole (4 hr, 75%) [75JCS(P1)345].

Diacetylation was observed when 4-amino-3-benzyltriazole was refluxed with acetic anhydride, giving 3-benzyl-4-diacetylaminotriazole (2 hr, 97%) [78JCS(P1)427].

In exploring the course of acetylation of several 4-amino-3-phenyl-1,2,3-triazoles, Sutherland and Tennant established guidelines for assigning the positions occupied by entering acetyl groups, by the use of IR and ¹H-NMR data [71JCS(C)706]. Their mildest conditions, stirring with an excess of acetyl chloride containing one tenth its volume of sulfuric acid (0–20°C, 1 day), gave

mainly the conventional result: monoacetylation of the 4-amino group. However, 4-amino-3-phenyltriazole-5-carboxamide produced 4-acetamido-3-phenyltriazole-5-*N*-acetylcarboxamide (68%). Acetic anhydride containing some sulfuric acid (20°C, 1 day) behaved similarly, except that 4-amino-3-phenyltriazole-5-carboxamide furnished a triacetylated product, 4-diacetyl-amino-3-phenyltriazole-5-*N*-acetylcarboxamide (**22**) (54%). Extraordinary results were obtained by these authors when 4-amino-3-phenyltriazole-5-carboxamide was refluxed with acetic anhydride (sulfuric acid absent). After 20 min, the principal product was 3-acetyl-4-anilino-triazole-5-carboxamide (70%), whereas prolonging the heating to 3 hr furnished 3-acetyl-4-anilino-triazole-5-*N*-acetylcarboxamide (**23**) (86%). Finally, after 12 hr of refluxing, the major product was 4-diacetyl-amino-3-phenyltriazole-5-*N*-acetylcarboxamide (56%). They concluded that acetylation favored a Dimroth rearrangement, but further acetylation promoted its retrogression [71JCS(C)706].

Other variants of acetylation are reported in Ref. 75G583 (on some 4-arylsulfonamidotriazoles), Ref. 78JCS(P1)427 (use of acetyl chloride with triethylamine), and Ref. 84LA1848 (another Dimroth rearrangement in refluxing acetic anhydride).

When the triazole contains both an aliphatic and an aromatic amino group, the former is acetylated preferentially. Thus 4-amino-5-aminomethyl-3-benzyltriazole, stirred with 1 Eq of acetic anhydride in pyridine, gave 4-amino-5-acetamidomethyl-3-benzyltriazole (20°C, 15 hr, 90%). The 1- and 2-methyl analogs were similarly made, but in aqueous pyridine, whereas the use of dry pyridine and 4 Eq of acetic anhydride acetylated both amino groups (75%). Acetic formic anhydride was used similarly to obtain either mono- or di-formylated products, as required [73JCS(P1)1634].

Partial deacetylation has been effected by refluxing with 50% acetic acid, whereby 4-diacetyl-amino-5-methoxycarbonyl-3-phenyltriazole produced the 4-monoacetyl analog (30 min, 90%). This method selectively removed acetyl from the 3 position, also from a 5-*N*-acetylcarboxamide group. Refluxing methanolic sodium hydroxide was used to deacetylate a 4-acetamido group, but this reagent hydrolyzed a 5-methoxycarbonyl substituent, and, when a 5-carboxamide group was present, it brought about cyclization to a 8-azapurin-6-one [71JCS(C)706].

The use of other acylating agents is illustrated by the following. 4-Amino-1-methyl-5-oxamoylaminomethyltriazole (**24**) (as tosylate salt), when refluxed in an excess of trifluoroacetic acid, produced 1-methyl-5-oxamoylaminomethyl-4-trifluoroacetamidotriazole (1 day, 83%) [81J(P1)887]. 4-Amino-5-aminomethyl-3-benzyltriazole and 1 Eq of trifluoroacetic anhydride in excess trifluoroacetic acid gave 4-amino-3-benzyl-5-trifluoroacetamidomethyltriazole (24°C, 8 hr, 67%); whereas replacing the acid by an excess of the anhy-

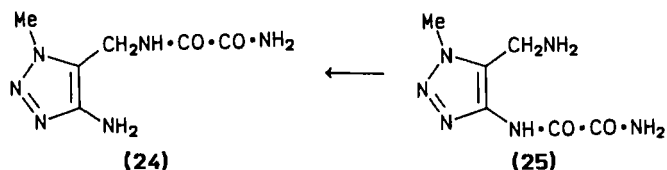
dride monoacylated both amino groups (24°C, 1 day, 85%) [78JCS(P1)513]. The trifluoroacetyl group was quickly removed from 4-amino-3-benzyl-5-(*N*-methyltrifluoroacetamidomethyl)triazole by boiling with *N* sodium hydroxide for 30 sec only (84%) [78JCS(P1)513].

For acylations with propionyl and phenylacetyl chlorides, see Ref. 71JCS(C)706. 4-Amino-5-phenyltriazole, refluxed with ethyl acetoacetate in toluene, gave 4-acetoacetamido-5-phenyltriazole (7 hr, 67%), which hot acetic anhydride converted to the 3-acetyl derivative. However, the reaction of 4-aminotriazole-5-carboxamide with cold acetoacetic ester gave a *N*-vinyl (and not a *N*-acyl) derivative (see Section III,B) [73JCS(P1)943].

4-Amino-5-aminomethyltriazoles formed the mono- or dicarbamates, as desired. Thus 4-amino-5-aminomethyl-1-methyltriazole, stirred with 1 Eq of ethyl chloroformate in *N*-sodium carbonate produced 4-amino-5-ethoxycarbonylaminomethyl-1-methyltriazole (20°C, 6 hr, 75%) (the 2-methyl analog was preferably made in ethanolic sodium hydroxide (70% yield), whereas the 3-benzyl analog, because of its poor solubility, was best formed in pyridine–chloroform (71% yield)). Ethoxycarbonylation of both amino groups occurred when an excess of the ester was used (50–70% yields). Stirring *S*-ethyl chlorothioformate with 4-amino-5-aminomethyl-3-benzyltriazole in pyridine gave 4-amino-3-benzyl-5-(ethylthio)carbonylaminomethyl triazole (20°C, 2 hr, 83%) [73JCS(P1)1634]. An example of the deacylation of carbamates is the formation of 4-aminotriazole hydrochloride when 4-ethoxycarbonylaminotriazole is refluxed with ethanolic potassium hydroxide (9 hr, 20%). The same product was obtained quantitatively by hydrogenation of 4-benzylloxycarbonylaminotriazole over palladium (20°C, 1 atm) (57YZ452).

Several oxalyl derivatives have been made, some of which behave remarkably. 4-Amino-5-aminomethyl-3-benzyltriazole, refluxed with diethyl oxalate in ethanol, gave 4-amino-3-benzyl-5-ethoxalylaminomethyltriazole (1 hr, 87%) [73JCS(P1)1634], and the 1-methyl analog was similarly formed (93%) [81JCS(P1)887]. Ethoxalyl chloride and 4-amino-3-benzyl-5-cyanotriazole, stirred in pyridine, formed 3-benzyl-5-cyano-4-ethoxalylaminotriazole (1°C, 1 hr, 90%), which, when stirred with 3 *N* ethanolic ammonia, gave the 4-oxamoylamino analog (20°C, 15 hr, 90%). Hydrogenation of the latter (over Raney nickel in ethanolic ammonia) gave 5-aminomethyl-1-methyl-4-oxamoylaminotriazole (**25**) (70°C, 7 hr, 4 atm, 51%). This underwent a most unusual rearrangement, when an ethanolic solution was acidified to –6°C, slow isomerization to 4-amino-1-methyl-5-oxamoylaminomethyltriazole (**24**) occurred (90%). The 3-benzyl analogs of these 1-methyltriazoles behaved similarly. The nature of the rearranged compounds was confirmed by synthesis and by the following physical data. Shift of an acyl group from the 4-amino to the 5-aminomethyl group was accompanied by a large fall in basic

strength (pK_a drops from 8 to 2). There is also a downfield shift in the ^1H -NMR spectrum of CH_2NH from δ 3.70 to 4.25 [81JCS(P1)887]. For the mono- and ditosylation of 4-aminotriazoles, see Ref. 75BSF1219.



2. *N*-Alkylations

Conditions for the selective alkylation of a 4-amino-1,2,3-triazole are often finely balanced. In the simpler case where the ring-nitrogen atoms carry no hydrogen atom, the 4-amino group alone is attacked. It is usual to alkylate it under basic conditions, after activation by formylation or trifluoroacetylation. This procedure usually gives an excellent yield of the monoalkyl derivative; dialkyl derivatives have been made only by incorporating a dialkylamino intermediate during ring synthesis (see Section IV). Alternatively, the aminotriazole may be quaternized in an aprotic polar solvent at an elevated temperature. The entering alkyl group then unites with a ring-nitrogen atom (with N-1 if the starting material is alkylated on N-3), and the primary amino group is spared.

In the other case where the ring-nitrogen atoms carry a (very mobile) hydrogen atom, the alkylation of aminotriazoles under basic conditions usually favors the ring nitrogens, and hence a mixture of the 1-, 2-, and 3-alkylated isomers is to be expected. Formation of 1-alkyl products can be suppressed by an electron-attracting substituent in the 5 position; 3-alkyl products are disfavored sterically by a substituent (even just a formyl group) on the 4-amino group. The relative acidic strengths of a 4-acylamido and a ring-NH group can influence selectivity. (Alternatively, the 4-amino group can be nitro-arylated under neutral conditions.) Selective N-methylation of a substituent in the 5 position of a 4-aminotriazole is described at the end of Section III,A,2,a.

a. Alkylation of a Primary Amino Group. 3-Benzyl-5-cyano-4-formamidotriazole and iodomethane, stirred with potassium carbonate in dimethylformamide, gave 3-benzyl-5-cyano-4-*N*-methylformamidotriazole (23°C, 1 day, 80%) [81JCS(P1)2344]. 4-Formamido-3-methyltriazole-5-carboxamide and dimethyl sulfate in *N* sodium hydroxide, gave 3-methyl-4-methylaminotriazole-5-carboxamide (20°C, 30 min, 65%) [68JCS(C)2076].

The 2-methyl isomer behaved similarly. In these examples, the formyl group is removed by the residual alkalinity, but in the following, one formyl group is lost before the reaction begins. 3-Benzyl-4-diformylaminotriazole-5-carboxamide and methyl sulfate in *N* sodium hydroxide gave 3-benzyl-4-methylaminotriazole-5-carboxamide (20°C, 50 min, 85%) [69JCS(C)152].

5-Cyano-4-tosylaminotriazole and methyl sulfate, in aqueous sodium carbonate (80°C, 3 hr), produced mainly 5-cyano-2-methyl-5-*N*-methyltosylaminotriazole, also six other methylated products, all separated by consecutive treatment with aqueous sodium carbonate (to remove traces of monoalkylated products), ether, and chromatography on silica gel (75LA2159).

4-Aminotriazole and picryl chloride (2,4,6-trinitrochlorobenzene), stirred in dimethylformamide, gave 4-picrylaminotriazole (*warning*: highly sensitive detonating agent) (25°C, 1 day, 76%). Treatment of this product with picryl fluoride produced 1-picryl-4-picrylaminotriazole (25°C, 1 day, 15%) (71JHC51).

Various 4-arylsulfonamidotriazoles, set aside with diazomethane in ether (0°C), were dimethylated: one methyl group combined with a nuclear nitrogen atom and the other with the exocyclic group (75G583). 4-Amino-3-benzyl-5-(methylthio)carbonyltriazole (**18b**), stirred with ethanolic methylamine, furnished 4-amino-3-benzyltriazole-5-*N*-methylcarboxamide (25°C, 45 hr, 94%) [78JCS(P1)513].

b. Alkylation of a Nuclear Nitrogen Atom by Replacement of Hydrogen. 4-Aminotriazole-5-carboxamide and methyl sulfate in methanolic sodium methoxide gave a 1:1 mixture of 4-amino-2- and -3-methyl-1,2,3-triazole-5-carboxamide (20°C, 30 min, 75%) [69JCS(C)152]. A more practical synthesis of the 2-methyl isomer utilized the anhydrodimer (**21**) of 4-formamidotriazole-5-carboxamide. To an aqueous suspension of this at 20°C, methyl sulfate was added during 45 min, while adjusting the pH to 9.5 with potassium hydroxide. The product, 4-formamido-2-methyltriazole-5-carboxamide, set aside in *N* sodium hydroxide, furnished 4-amino-2-methyltriazole-5-carboxamide (90%) [68JCS(C)2076]. The same anhydrodimer (**21**), benzyl chloride, and potassium carbonate, heated in dimethylformamide, gave 2-benzyl-4-formamidotriazole-5-carboxamide (90°C, 3 hr, 75%) [72JCS(P1)468]. These alkylations provided a gateway for entering the 2-methyl- and 2-benzyl-1,2,3-triazole series.

4-Amino-5-cyanotriazole and dimethyl sulfate, heated in aqueous sodium hydroxide, produced a mixture of the 1-, 2-, and 3-methyl derivatives (60°C, 20 hr, 81%), in which the 2-isomer was most strongly represented and the 1-isomer, least). The products were separated on silica by thin-layer chromatography (75BSF1219). 4-Dimethylamino-5-phenyltriazole,

propiolactone, and sodium ethoxide, stirred in dimethylformamide, produced 3-(4-dimethylamino-5-phenyltriazol-2-yl)propionic acid (0°C, 15 hr, 41%) (78JMC1254).

The synthesis of *N*-ribofuranosyltriazoles, for use as metabolite analogs of the purine-forming imidazoles, provides a different aspect of *N*-alkylation in the triazole series. Acid-catalyzed fusion of 4-nitrotriazole with tetra-*O*-acetyl- β -D-ribofuranose gave 2- β -D-ribofuranosyl-4-nitrotriazole (175°C, 45 min, 58%), accompanied by 24% yield of the 1-ribofuranosyl isomer. The acetyl groups were removed with cold methanolic sodium methoxide (85% yield), and the nitro group reduced to a primary amine with hydrazine hydrate over palladium in methanol (25°C, 93%) (72JHC1195).

4-Aminotriazole, and some of its 5-substituted derivatives, when fused with 1,2,3,5-tetra-*O*-acetyl- or -benzoyl- β -D-ribofuranose, gave a 1:1-mixture of 2- and 3-ribofuranosyltriazoles (76USP3968103). 4-Acetamidotriazole-5-carboxamide, mercuric cyanide, and tri-*O*-benzoyl- β -D-ribofuranosyl chloride, when refluxed in nitromethane, furnished 4-acetamido-1-(2, 3, 5-tri-*O*-benzoyl- β -D-ribofuranosyl)triazole-5-carboxamide (3 hr, 48%), from which the benzoyl groups were removed in methanolic ammonia (0°C, 3 days, 54%) (72BCJ2577). Occupation of the 1 position in this and other ribosylations was unexpected but was carefully verified.

c. *Quaternization; Debenzylation.* Wiley and Moffat showed that methyl iodide reacted with 1-benzyltriazole to produce the same substance as did benzyl iodide with 1-methyltriazole (1-methyl-3-benzyltriazolium iodide) (55JA1703). Thus there is no tendency for the 2 position to become quaternized. In the belief that this knowledge could provide the first practical entry into the 4-amino-1-methyltriazole series, 4-amino-3-benzyltriazole-5-carboxamide and methyl toluene-*p*-sulfonate were briefly heated at 150°C, and gave 4-amino-3-benzyl-5-aminocarbonyl-1-methyl-1,2,3-triazolium toluene-*p*-sulfonate (70% yield) [68JCS(C)344; 73JCS(P1)2659]. Conditions for success are critical, and as this has become the key intermediate for introducing a methyl group into the 1 position of a 4-aminotriazole, the following unpublished details are offered. The total heating time may vary from 3 to 6 min, but observation of the appearance is more important. The final color should be a rich golden (but not dark) brown, and the effervescence should be decreasing but not ended. Vigorous hand stirring throughout is essential. Purification should begin with boiling the crystals (formed on cooling) with 20 parts of ethanol, chilling, and discarding the filtrate (85MI2).

Because a 3-benzyl group is often used for protection during synthesis or transformation of the 4-aminotriazoles, the need for debenzylation often arises. This operation can be vigorously reductive because the 1,2,3-triazole nucleus resists reduction. The most used debenzylation method is that of

Hoover and Day. In this, the triazole is stirred with liquid ammonia while small pieces of sodium are added until a faint blue color persists. This color is discharged with a little ammonium chloride, and the solvent is allowed to evaporate overnight. After the toluene formed in the reaction has been removed under vacuum, the remaining white sodium salt is dissolved in a little ice water. The highly alkaline solution is acidified with hydrochloric acid and the product filtered. In this way, these authors debenzylated the 4-amino-3-benzyl derivatives of 1,2,3-triazole (37%), and its 5-carboxamide (66%), 5-carboxyhydrazide (50%), and 5-nitrile (86% yields) (56JA5832).

The following alternative work-up was found to overcome the retention of toluene by the ammonia-freed residue, and to increase yields. This residue was rubbed with ice and water, and the pH lowered to 6 with 8 *M* phosphoric acid. The mixture was then taken to dryness on a rotary evaporator. The residue was rubbed with a little water, and the product filtered. This modification was applied to the production of all of the above examples and to 5-cyano-4-methylaminotriazole (90%) [81JCS(P1)2344] and 4-methylaminotriazole-5-carboxamide (85%) [69JCS(C)152]. In all of these examples, each addition of sodium to the ammonia produced a transient blue color, attributed to solvated electrons (from the sodium) trapped in a cage of ammonia molecules (80MI2). However, in the debenzylation of 4-amino-3-benzyl-5-cyanotriazole, only a red color was seen [73JCS(P1)1629], whereas 4-amino-3-benzyl-5-phenyltriazole gave a green color [71JCS(C)2156]. For the isolation of free 4-aminotriazole after debenzylation, see Ref. 73TL1137.

As an alternative to the use of sodium, hydrogenation in ethanolic ammonia over palladium is effective. Thus 4-amino-5-aminocarbonyl-3-benzyl-1-methyl-1,2,3-triazolium toluene-*p*-sulfonate gave 4-amino-1-methyltriazole-5-carboxamide (75°C, 4 atm, 3 hr, 82%) [68JCS(C)344; 72JCS(P1)461]. 4-Amino-3-benzyltriazole-5-*N*-butylcarboxamidine was similarly debenzylated (70°C, 3 hr, 85%) [74JCS(P1)2030].

B. OTHER REACTIONS OF THE 4-AMINO GROUP

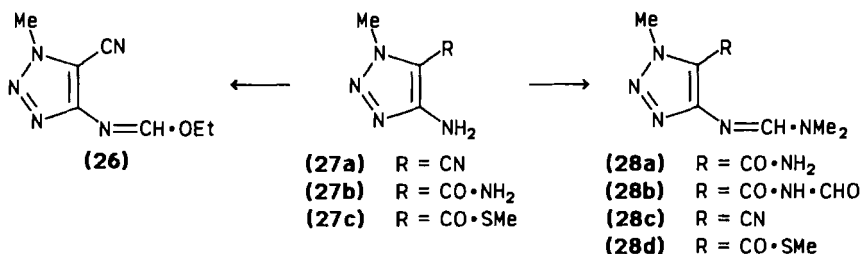
Even when strong hydrogen bonding to a substituent in the 5 position prevents a 4-aminotriazole from being acylated [73JCS(P1)2037], the primary amino group can still be incorporated into amidine or imidate structures. These can serve as protective groups during further reactions, or even form part of a new ring (Section III,B,1). The 4-amino group can also be modified by reactions that are based on diazotization (Section III,B,2). Although Vilsmeier reactions usually fail when a primary amino group is present, some 4-aminotriazoles can incorporate an aldehyde group in the 5-position (Section III,B,3).

1. Reactions Leading to a $\text{N}=\text{C}-\text{O}$ or $\text{N}=\text{C}-\text{N}$ Structure

4-Amino-5-cyano-1-methyltriazole (**27a**), triethyl orthoformate, and a little acetic anhydride, boiled vigorously, gave 5-cyano-4-ethoxymethylenamino-1-methyltriazole (**26**) (4 hr, 78%). (Because the reaction is driven by loss of ethanol, the apparatus is best set up for slow, fractional distillation). An excess of acetic anhydride contaminated the product with an acetyl derivative of the starting material. The 2-methyl, 3-methyl, and 3-benzyl analogs were prepared similarly, the last-named in 90% yield. The parent, 4-amino-5-cyanotriazole, gave a mixture of products. These amidates became hydrolyzed in moist air to, e.g., 5-cyano-4-formamido-1-methyltriazole. They proved to be valuable intermediates for synthesizing 6-imino-1-methyl-1,6-dihydro-8-azapurines [73JCS(P1)2659].

The story of the $\text{N}=\text{C}-\text{N}$ structures is a little more complex. 4-Amino-1-methyltriazole-5-carboxamide, stirred with dimethylformamide and a little phosphoryl chloride, gave 4-dimethylaminomethylenamino-1-methyltriazole-5-carboxamide (**28a**) (25°C, 2 hr, 54%) and a trace of its 5-*N*-formyl derivative (**28b**). A larger proportion of phosphoryl chloride converted the amide group to a carbonitrile (**28c**). For example, 4-amino-3-methyltriazole-5-carboxamide, dimethylformamide, and an excess of phosphoryl chloride produced 5-cyano-4-dimethylaminomethylenamino-3-methyltriazole (**28c**) (25°C, 2 hr, 85%). The 3-benzyl analog reacted similarly (92% yield). Unfortunately, the crude 1- and 2-methyl analogs were contaminated with the relevant diacylamide, e.g., **28b** (6%). From the crude 2-methyl product, the diacylamide was removed by its insolubility in hot benzene (yield of nitrile, 85%). The 1-methyl product required chromatography (yield 60% of **28c**). Fortunately, when hydrolysis to 4-amino-5-cyano-1-methyltriazole was the intended next step, the crude mixture could be advantageously used [72JCS(P1)461; 85MI2]. The diacylamides, e.g., **28b**, because of the acidic nature of the NH group, dissolved in cold 0.1 *N* sodium hydroxide, but these solutions soon deposited the primary amides quantitatively (**28a**).

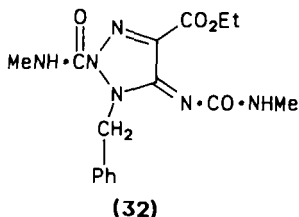
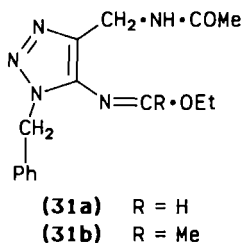
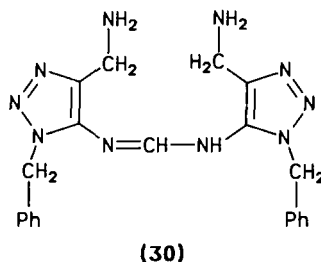
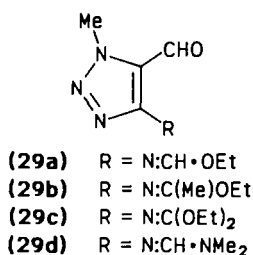
Hydrolysis of these 4-dimethylaminomethylenamino nitriles to the



corresponding 4-amino nitriles occurred on refluxing with 2 *N* hydrochloric acid (15 min, 80–90%) [73JCS(P1)1634]. 4-Amino-3-methyltriazole-5-carboxamide could be converted to 4-amino-5-cyano-3-methyltriazole in a one-pot procedure in which, after the dimethylformamide had reacted, the mixture was refluxed with *N* hydrochloric acid for 5 min (yield, 80%) [69JCS(C)2379]. The 3-benzyl analog was converted similarly (90%) [70JCS(C)230], but this process turned out to be destructive for the 1- and 2-methyl analogs.

In a related reaction, 4-amino-1-methyl-5-(methylthio)carbonyltriazole (27c), when warmed with dimethylformamide and phosphoryl chloride, gave 4-dimethylaminomethylenamino-1-methyl-5-(methylthio)carbonyltriazole (28d) (85°C, 30 min, 80%), which ethanolic ammonia converted to the corresponding amide (28a) (25°C, 18 hr, 99%) [72JCS(P1)461].

Although the 4-aminotriazole-5-carbaldehydes resist *N*-acylation, they readily undergo condensations of this kind [73JCS(P1)2037]. 4-Amino-1-methyltriazole-5-carbaldehyde, heated with triethyl orthoformate, gave 4-ethoxymethylenamino-1-methyltriazole-5-carbaldehyde (29a) (120°C, 3 hr, 72%), and the 3-benzyl analog was obtained similarly (82%). With triethyl orthoacetate, the product was 4-(α -ethoxyethylidenamino)-1-methyltriazole-5-carbaldehyde (29b) (79%); 2-methyl and 3-benzyl analogs were similarly prepared. With tetraethyl orthocarbonate, 4-diethoxymethylenamino-1-methyltriazole-5-carbaldehydes of type 29c were produced. Finally, 4-amino-1-methyltriazole-5-carbaldehyde, stirred with dimethylformamide and phosphoryl chloride, gave 4-dimethylaminomethylenamino-1-methyltriazole-5-



carbaldehyde (**29d**); 2-methyl and 3-benzyl analogs were also prepared in this way (25°C, 10 hr, 80%) [73JCS(P1)2037].

4-Amino-5-aminomethyl-3-benzyltriazole acetate, when heated with triethyl orthoformate, produced *N,N'*-bis-(5-aminomethyl)-3-benzyltriazol-5-ylformamidine (**30**) (100°C, 1 hr, 90%). The same starting material, but as the free base, heated with triethyl orthoformate and acetic anhydride, gave 5-acetamidomethyl-3-benzyl-4-ethoxymethylenaminotriazole (**31a**) (100°C, 1 hr, 80%); triethyl orthoacetate similarly made the homolog **31b** (50%) [76JCS(P1)291].

4-Amino-3-benzyl-5-ethoxycarbonyltriazole and methyl isocyanate, when stirred with a trace of potassium hydroxide in chloroform, gave, surprisingly, 4-*N*-methylcarbamoylimino-3-benzyl-5-ethoxycarbonyl-2-*N*-methylcarbamoyl- Δ^3 -triazoline (**32**) (25°C, 4 days, 48%) (69CB3698).

2. Reactions Involving N—N Structures

4-Aminotriazole-5-carboxamide, diazotized with isopentyl nitrite in dilute acetic acid, gave the remarkably stable 5-diazotriazole-4-carboxamide (5°C, 1 hr, 52%), which withstood recrystallization from boiling water (61JOC2396). Among examples of diazo deamination, 5-acetamido-4-amino-3-benzyltriazole was quantitatively converted to the diazonium fluoroborate, which was stirred with sodium borohydride in methanol (0°C, 15 min, 30%) to furnish 5-acetamido-3-benzyltriazole (72JOC4124). 4-Amino-2- β -D-ribofuranosyltriazole was deaminated with sodium nitrite in hypophosphorus acid (35°C, 30 min, 50%) (72JHC1195).

Among conversions of the amino to the azido group, 4-amino-2-phenyl-5-phenylazotriazole, treated in turn with hydrochloric acid, sodium nitrite, and sodium azide, produced 4-azido-2-phenyl-5-phenylazotriazole (0°C, 30 min, 76%) (70BCJ3587); 4-amino-5-methoxycarbonyl-3-phenyltriazole, similarly treated, gave the 4-azido analog (82%) (83BSB913).

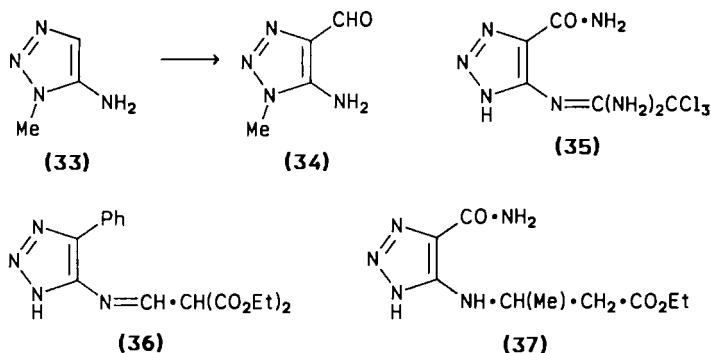
4,5-Diamino-2-phenyltriazole and nitrosobenzene, stirred in an emulsion of benzene and 12 *N* sodium hydroxide, gave 4-amino-2-phenyl-5-phenylazotriazole (60°C, 10 min, 72%) (70BCJ3587). Potassium permanganate in dilute acetic acid oxidized 4-amino-3,5-diphenyltriazole to 3,3',5,5'-tetraphenyl-4,4'-azotriazole (25°C, 30%). This product, stirred with hydrazine hydrate and palladized carbon in chloroform, gave 4-amino-3,5-diphenyltriazole (25°C, 1 hr, 91%) (70JOC2215).

3. Miscellaneous

A rare example of the Vilsmeier–Haack reaction succeeding with a primary amine is provided by 4-amino-3-methyltriazole (**33**), which, when heated

with dimethylformamide and phosphoryl chloride, was converted to 4-dimethylaminomethylenamino-5-formyl-3-methyltriazole, an isomer of **29d** (85°C, 1 hr, 75%). This product, refluxed with *N* hydrochloric acid, gave 4-amino-5-formyl-3-methyltriazole (**34**) (20 min, 65%). The 3-benzyl analog was made similarly. This procedure converted 4-amino-1-methyltriazole only to 4-dimethylaminomethylenamino-1-methyltriazole (98%) [78JCS(P1)427]. An attempted Friedel–Crafts reaction on several nuclear-alkylated 4-amino-triazoles, using dichloromethyl methyl ether and stannic chloride in dichloromethane, succeeded only in formylating the amino group [78JCS(P1)427].

4-Aminotriazole-5-carboxamide, trichloroacetamidine, and acetic acid, refluxed in ethanol, gave 4-(α -amino- β,β,β -trichloroethylidinaminotriazole-5-carboxamide (**35**) (24 hr, 82%). Several N-alkylated 4-aminotriazoles behaved similarly. With other amidines, the reaction did not stop at this stage but produced an 8-azapurine [79JCS(P1)922].



4-Amino-5-phenyltriazole, when refluxed with diethyl ethoxymethylmalonate and acetic acid in benzene, produced 4-(2-diethoxycarbonylvinylamino)-5-phenyltriazole (**36**) (30 hr, 64%) [71JCS(C)2156]. 4-Aminotriazole-5-carboxamide and ethyl acetoacetate, stirred with acetic acid and dimethylformamide, provided 4-(2-ethoxycarbonyl-1-methylvinylamino)triazole (**37**) (20°C, 16 hr, 50%) [73JCS(P1)943].

For the employment of 4-aminotriazoles in the synthesis of bicyclic heterocycles, see Section V,B.

C. REACTIONS OF GROUPS IN THE 5 POSITION OF 4-AMINOTRIAZOLES

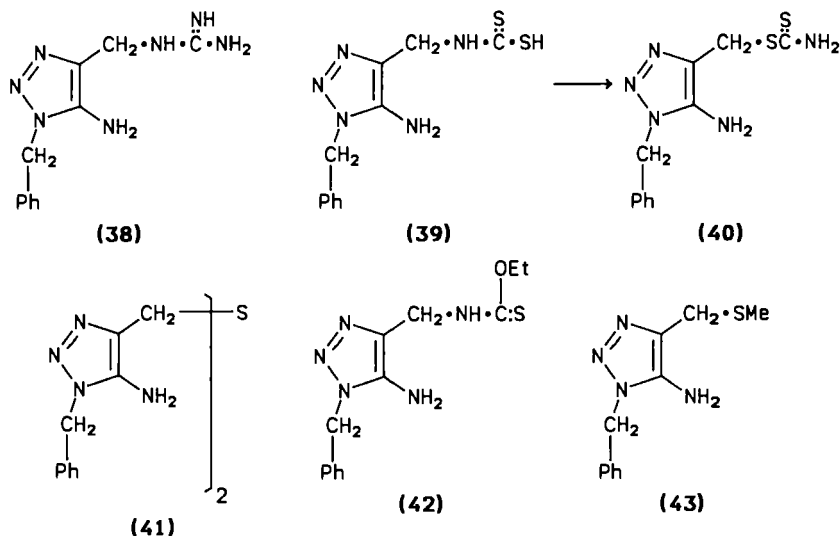
The presence of an amino group in the 4 position of a 1,2,3-triazole can affect the reactivity of a 5 substituent by electronic or steric effects, or by hydrogen bonding.

1. Reactions of Aminoalkyl and Hydroxyalkyl Groups

Reactions that affect both amino groups in 4-amino-5-aminomethyl-triazoles have been dealt with in Sections III,A,1 and III,B,1. In the following examples, only the aminomethyl group reacts.

4-Amino-5-aminomethyl-3-benzyltriazole and *S*-methylisothiuronium acetate, refluxed in ethanol, gave the acetate of 4-amino-3-benzyl-5-(guanidinomethyl)triazole (**38**) (1 hr, 75%) [80JCS(P1)2918]. 4-Amino-3-benzyl-5-(trifluoroacetamidomethyl)triazole, when stirred with iodomethane and potassium carbonate in dimethylformamide, afforded 4-amino-3-methyl-5-(*N*-methyltrifluoroacetamidomethyl)triazole (24°C, 1.5 hr, 74%) [78JCS(P1)513].

4-Amino-5-aminomethyl-3-benzyltriazole, heated with carbon disulfide and ammonia in ethanol, produced ammonium *N*-(4-amino-3-benzyltriazol-5-ylmethyl)dithiocarbamate (**39**) (20°C, 2 hr, 70%). Repeating this preparation in water gave the isomer **40**, although this transfer of a methylene group from nitrogen to sulfur reverses the usual direction. Other examples of the N → S shift are in the same publication [80JCS(P1)2009]. When **39** was heated under reflux with ethanolic sodium ethoxide, the sulfide **41** was obtained (2 hr, 37%). Again, **39** was converted by iodomethane to its *S*-methyl ester (20°C, 3 hr, 84%), which, on attempted recrystallization from 1:1 ethanol–water, gave *O*-ethyl *N*-(4-Amino-3-benzyl-1,2,3-triazol-5-ylmethyl) monothiocarbamate (**42**), by ethanolysis. If, however, this *S*-methyl ester was refluxed with ethanolic sodium ethoxide, 4-amino-3-benzyltriazol-5-ylmethyl methylsulfide (**43**) was obtained [80JCS(P1)2009].



A 4-amino-5-hydroxymethyltriazole, obtainable by reduction of an ester, can readily be oxidized to the aldehyde. 4-Amino-5-hydroxymethyl-2-methyltriazole, stirred in chloroform with manganese dioxide, provided 4-amino-5-formyl-2-methyltriazole (20°C, 2.5 hr, 71%). The 3-benzyl analog responded similarly (78%) [73JCS(P1)1629].

2. *Reactions of Aldehydes*

The preparation and reactions of the azine, phenylhydrazone, and phenyl-semicarbazone of 4-amino-5-formyl-2-methyltriazole proceeded normally. One acetal has been prepared as follows. 4-Amino-3-benzyl-5-formyltriazole and boron trifluoride (as diethyl ether complex), stirred in methanol, gave 4-amino-3-benzyl-5-dimethoxymethyltriazole (20°C, 6 hr, 53%) and a dimeric by-product, 4-amino-3-benzyl-5-(3-benzyl-5-dimethoxytriazol-4-ylimino-methyl)triazole [73JCS(P1)2037]. The amino group in 4-aminotriazole-5-carbaldehydes lends itself readily to the formation of amidines and imidates (Section III,B,1), but it resists acylation.

3. *Reactions of Carboxylic Acids, Esters, and Amides*

4-Amino-2-methyltriazole-5-carboxylic acid [68JCS(C)2076] resisted all attempts at decarboxylation; regrettably so, because the product is expected to have physical properties that contrast with those of its isomers (Tables I, II, and III). On the other hand, 4-amino-3-methyltriazole-5-carboxylic acid, refluxed in butanol, produced 4-amino-3-methyltriazole (3 hr, 65%) [69JCS(C)2379], and the 1-methyl isomer, heated under nitrogen, gave 4-amino-1-methyltriazole [210°C, 15 min, 83%] [73JCS(P1)1629]. 4-Amino-3-benzyltriazole-5-carboxylic acid, when refluxed in pyridine (10 min), furnished a mixture of 4-amino-3-benzyltriazole (75%) and 4-benzylaminotriazole (20%), the latter by rearrangement [70JCS(C)230].

Some acid-catalyzed decarboxylations are recorded. 4-Aminotriazole-5-carboxylic acid, refluxed in dilute hydrochloric acid, gave 5-aminotriazole hydrochloride (1 hr, 57%); 4-amino-3-cyclohexyltriazole-5-carboxylic acid similarly gave 4-amino-3-cyclohexyltriazole (1 hr, 63%) [71JCS(C)1501].

Although esters can be obtained by primary synthesis (56JA5832), the following may be the sole example of an esterification in this series. 4-Amino-2-methyltriazole-5-carboxylic acid and sulfuric acid, refluxed in methanol, formed the methyl ester (7 hr, 91%) [73JCS(P1)1629].

The esters of 4-aminotriazole-5-carboxylic acids have been little explored. Ethyl 4-anilino-5-carboxylate and ethanolic potassium hydroxide furnished the corresponding acid (no details, 77%) (57JOC654). Ethyl

3-benzyl-4-aminotriazole-5-carboxylate was reported as "resistant to hydrolysis" (no details), and its conversion to the carboxamide required heating with ammonia-saturated ethylene glycol in an autoclave (100°C, 24 hr, 67%). However, it was readily converted to the hydrazide by warming with hydrazine hydrate (97°C, 4 hr, 97%) (56JA5832).

Several ethoxalylamides (NHCOCOOEt) were readily converted to oxamoylamides (NHCOC(=O)NH₂). For example, 3-benzyl-5-cyano-4-ethoxalylaminotriazole, stirred with 3 *N* ethanolic ammonia, was converted to 3-benzyl-5-cyano-4-oxamoylaminotriazole (20°C, 15 hr, 90%); similar treatment of the 1-methyl analog gave a 92% yield. 4-Amino-3-benzyl-5-ethoxalylaminomethyltriazole similarly gave 4-amino-3-benzyl-5-oxamoylaminomethyltriazole (an analog of **24**) (25°C, 8 hr, 93%) [81JCS(P1)887].

The esters have also been reduced to alcohols, e.g., methyl 4-amino-2-methyltriazole-5-carboxylate and lithium aluminum hydride, stirred in tetrahydrofuran, produced 4-amino-5-hydroxymethyl-2-methyltriazole (20°C, 6 hr, 60%), and the 3-benzyl analog gave 70% [73JCS(P1)1629].

The hydrolysis of amides in this series has encountered some difficulties, such as slowing of the reaction by formation of an insoluble sodium salt (a switch to potassium hydroxide often helped). Alkaline conditions favor the Dimroth rearrangement, although this is possible only when the 3 position is substituted (Section III,D). When the rearrangement is allowed, and it is greatest for the 3-phenyl, less for 3-benzyl, least for 3-methyl groups, two isomers have to be separated. As, in the present case, these will both be acids, an insoluble salt of one of them has usually been sought.

4-Amino-1-methyltriazole-5-carboxamide, heated with *N* potassium hydroxide, gave the corresponding acid (98°C, 1 hr, 74%) [72J(P1)449]. The 2-methyl isomer required 4 hr (92%) [68JCS(C)2076]. 4-Aminotriazole-5-carboxamide, which is an acid, proved less susceptible to attack by the hydroxyl anion because of the Coulombic effect. However, it was largely converted to the corresponding acid when heated with 10 *N* sodium hydroxide (polypropylene flask) (98°C, 8 hr, 85%) [68JCS(C)2076].

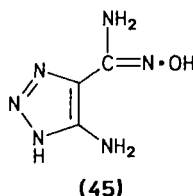
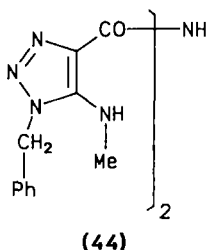
A rather surprising product was furnished when 3-benzyl-*N*-methylformamidotriazole-5-carboxamide (**17**) was refluxed with ethanolic sodium ethoxide, namely, bis-(3-benzyl-4-methylaminotriazole-5-carbonyl)amine (**44**) (1 hr, 15%) [81JCS(P1)2344]. An unwanted incorporation of the solvent was found when 4-aminotriazole-5-carboxamide and thionyl chloride were stirred in pyridine, giving 4-amino-*x*-(*y*-pyridyl)-1,2,3-triazole-5-carbonitrile (4°C, 8 hr, 25%) [73JCS(P1)1629].

Some miscellaneous reactions, related to the hydrolysis of amides, follow. 1-Methyl-4-ureidotriazole-5-carboxylic acid, refluxed with *N* potassium hydroxide, gave 4-amino-1-methyltriazole-5-carboxylic acid (3 hr, 43%)

[72JCS(P1)449]. 4-Aminotriazole-5-carbamidoxime (**45**), as hydrochloride, heated with water under pressure, produced 4-aminotriazole-5-carboxamide (150°C, 8 hr, 39%). The same amidoxime, hydrogenated in aqueous potassium carbonate over Raney nickel, furnished 4-aminotriazole-5-carboxamidine (40°C, 1 atm, 6 hr, 41%) (60JA3189).

4-Amino-5-(methylthio)carbonyltriazoles (such as **18** and the related nuclear N-methylated compounds) were converted in 14 *N* aqueous ammonia to the corresponding carboxamides (22°C, 2 days, 90%); also, similarly, to the *N*-methylcarboxamides (80–97%). Boiling aqueous *N* sodium carbonate produced the corresponding carboxylic acids (1 hr, 80–92%) [69JCS(C)2379; 78JCS(P1)513].

The most convenient synthesis of nitriles in this series is by dehydration of carboxamides with phosphoryl chloride. The two-stage process by which this is effected was discussed in Section III,B,1.



To initiate a Curtius rearrangement, 4-amino-3-benzyltriazole-5-carboxyhydrazide was treated with sodium nitrite in dilute hydrochloric acid, giving the azide (5°C, 74%), which, when refluxed in ethanol, furnished 4-amino-3-benzyl-5-ethoxycarbonylaminotriazole (20 hr, 52%). This carbamate, refluxed in ethanolic sodium hydroxide, produced 1-benzyl-4,5-diaminotriazole (3 hr, 55%). A Schiff base, 4-amino-5-benzylidenamino-3-benzyltriazole, was deposited when benzaldehyde was added to an ethanolic solution of the above diamine (25°C, 90%) (72JOC4124).

4. Reactions of Nitriles. Dimerizations

Some hydrolyses will first be described, then the preparatively important reductions, and finally some addition reactions. 5-Cyano-4-formamido-2-methyltriazole, refluxed with trifluoroacetic acid, gave 4-formamido-2-methyltriazole-5-carboxamide (1 hr, 85%). The same nitrile, set aside in 2 *N* sodium hydroxide was hydrolyzed to 4-amino-2-methyltriazole-5-carboxamide (25°C, 15 hr, 95%) [73JCS(P1)2659].

5-Cyano-4-dimethylaminomethylenamino-1-methyltriazole, in alkaline hydrogen peroxide solution, yielded the amide (25°C, 12 hr, 87%)

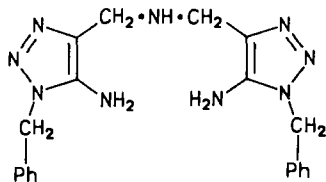
[72JCS(P1)461]. 3-Benzyl-5-cyano-4-methylaminotriazole, heated with hydrogen peroxide and ethanolic sodium hydroxide, similarly gave the amide (65°C, 1 hr, 75%) [81JCS(P1)2344].

5-Cyano-2-methyl-4-*N*-methyltosylaminotriazole, in ethanolic hydrogen chloride, gave ethyl 2-methyl-4-*N*-methyltosylaminotriazole-5-carboxylate (25°C, 20 hr, 78%). Alkaline hydrolysis of this ester produced the carboxylic acid (74%), which was quantitatively decarboxylated by refluxing in diethylene glycol (5 hr) (75LA2159).

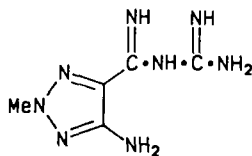
4-Amino-5-cyano-1-methyl- (also 2-, and 3-methyl- and 3-benzyl)triazole were hydrogenated (20°C, 1 atm) over palladium in (about 0.1 *M*) hydrochloric acid; the initially formed imonium cation was hydrolyzed faster than the desired product (4-amino-5-formyl-*x*-alkyltriazole) was polymerized by the acid. Yields ranged from 42 to 92%. Preparatively, this is a convenient method but can become inconveniently bulky when scaled up; in that case, it is better to oxidize the corresponding alcohol [73JCS(P1)1629]. Similar hydrogenation of 4-amino-5-cyanotriazole gave a mixture of unstable products. Catalytic hydrogenation of 4-amino-5-cyano-2-methyltriazole in 50% acetic acid, in the presence of aldehyde-trapping reagents, gave about 65% yields of the phenylhydrazone, the azine, and the phenylsemicarbazone, from which the required aldehyde could not be liberated [73JCS(P1)1629].

Hydrogenation of 1-, 2-, and 3-methyl- (also 3-benzyl-)4-amino-5-cyanotriazoles over Raney nickel in ethanolic 3 *N* ammonia gave the corresponding 5-aminomethyl compounds (70°C, 4 atm, 4 hr, 60–80%). The products, which attract carbon dioxide from the air and some of which are hygroscopic, are conveniently purified and stored as phosphates. The parent, 4-amino-5-cyanotriazole, was decomposed by this reduction. Neither sodium in ethanol nor lithium aluminum hydride effected this reduction on any of the cyanotriazoles. When ammonia was omitted, secondary amines were obtained, e.g., bis-(4-amino-3-benzyl-1,2,3-triazol-5-ylmethyl)amine (46) [73JCS(P1)1634; 81JCS(P1)2344]. If the 4-amino group is acylated before hydrogenation, the acyl group may migrate to the aminomethyl group as soon as the reaction mixture is acidified (see Section III.C,1).

4-Amino-3-benzyl-5-cyanotriazole, in ethanol saturated with hydrogen chloride, gave ethyl 4-amino-3-benzyltriazole-5-formimidate



(46)

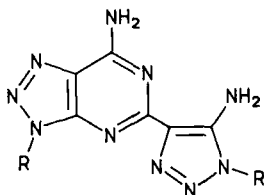


(47)

[74JCS(P1)2030]. 4-Amino-5-cyano-2-methyltriazole, refluxed with free guanidine in ethanol, was converted to 1-(4-amino-2-methyl-1,2,3-triazol-5-ylcarbonimidoyl)guanidine (**47**) (1 hr, 85%). The 3-benzyl analog was made similarly (65%) [75JCS(P1)345].

Hydrogen sulfide, bubbled through a solution of 4-amino-3-benzyl-5-cyanotriazole and trimethylamine in pyridine, produced 4-amino-3-benzyltriazole-5-thiocarboxamide (24°C, 24 hr, 81%) [77JCS(P1)210].

4-Amino-3-benzyl-5-cyanotriazole, refluxed with ethanolic potassium hydroxide, gave the dimer **48a** (1 hr, 40%) as well as 4-amino-3-benzyltriazole-5-carboxamide (55%) [70JCS(C)230]. A similar dimer (**48b**) was obtained when malononitrile and phenyl azide were stirred in ethanolic sodium ethoxide (0°C, 24 hr, 71%) [71JCS(C)706]; malononitrile, similarly treated with *p*-azidophenylacetic acid, gave **48c** (79FES371). A 4-amino-5-cyanotriazole is an intermediate in each case.



(**48a**) R = CH₂Ph

(**48b**) R = Ph

(**48c**) R = C₆H₄-*p*-CH₂CO₂H

D. RING OPENINGS AND REARRANGEMENTS

Two rearrangements have already been discussed: (1) the migration of an acyl group from the aromatic to the aliphatic nitrogen atom in 4-amino-5-aminomethyltriazoles, as illustrated by the change **25** → **24** (Section III,A,1), and (2) the transfer of a methylene group (in a 5-aminomethyl substituent) from a nitrogen to a sulfur atom, as exemplified by the change **39** → **40** (Section III,C,1).

1. Ring-Chain Tautomerism

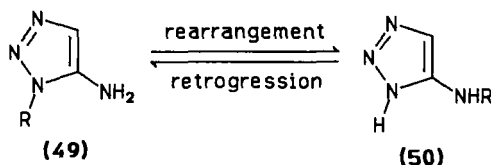
N,N-Diethylpropyn-1-ylamine (Et₂NC≡CMe), when stirred in ether with methylsulfonyl azide (MeSO₂N₃), gave an equilibrium mixture of 4-diethylamino-5-methyl-3-methylsulfonyltriazole (63%) and *N,N*-diethyl-*N'*-methylsulfonyl-2-diazopropionamidine (37%; equilibrium data, yields not given) (0°C, 30 min). The triazole form is favored by substituents exhibiting

+*M* and +*I* effects (73LA1505). The same acetylene and benzenesulfonyl azide, similarly gave a 3:2 equilibrium mixture of 4-diethylamino-5-methyl-3-benzenesulfonyltriazole and *N,N*-diethyl-*N'*-benzenesulfonyl-2-diazopropionamidine [$\text{Et}_2\text{NC}(\text{CMeN}_2)\text{NSO}_2\text{Ph}$]. Thirteen analogs were also described in which the proportion of isomers varied from 96:4 to 5:95; no yields were given (70TL2823). Diphenylaminoacetylene, stirred in ether with *p*-dimethylaminobenzenesulfonyl azide (7 days, 25°C), produced 4-diphenylamino-3-*p*-dimethylaminobenzenesulfonyltriazole in equilibrium with some *N,N*-diphenyl-*N'*-*p*-dimethylaminobenzenesulfonyl-2-diazoacetamidine [$\text{Ph}_2\text{NC}(\text{CHN}_2)\text{NSO}_2\text{C}_6\text{H}_4\text{-}p\text{-NMe}_2$] (72CB2963).

Studies along lines similar to those of this German work, carried out in the United States, led to similar results. In addition, it was shown that 1-(*N,N*-dimethylamino)-2-phenylacetylene gave phenylacetamidines with little tendency to tautomerize to triazoles (70JOC3444). 4-Aminotriazole has been shown not to take part in ring-chain tautomerism (73TL1137).

2. The Dimroth Rearrangement and Its Retrogression

Both 3-aryl-4-aminotriazoles (**49**) and 4-arylaminotriazoles (**50**) are thermally unstable and can be transformed (without appreciable loss) to an equilibrium mixture of both isomers. This rearrangement (**49** → **50**) is named after Otto Dimroth, who discovered it and its retrogression (**50** → **49**) (09LA183; 10LA127). These reactions have been reviewed recently [84CHC(5)669, pp 694–697], and a fuller discussion is available (68M11). The following summary of the controlling factors should help the preparative chemist who, in setting out to synthesize a compound of type **49**, could inadvertently end with its isomer (**50**), also vice versa. By drawing attention to the opposing effect of alkyl and aryl groups (as *R* in **50**), the summary will indicate how control over these reactions has opened a new vista in triazole synthesis.



The Dimroth rearrangement is possible only for those triazoles that carry a substituent in the 3 position; also a retrogression can restore the mobile group only to the 3 position. With the aid of ^{15}N , it was shown that the reaction is monomolecular; the ring opens and (after rearrangement) closes to a secondary amine (**50**) (61NL828). It is generally agreed that the intermediate

is a diazotate anion (e.g., $^-\text{NO}=\text{NCH}_2\text{C}(\text{NH}_2)=\text{NPh}$), a structure similar to that suggested by Dimroth. However, when the rearrangement is effected by UV radiation, the intermediate seems to be a diirine, e.g., **19** (see Section II, G).

Dimroth, who worked only with the 3-phenyltriazoles, concluded that hot, basic solutions convert these quantitatively to the secondary amines **50**. Noting that the weak base pyridine was as effective as the stronger ethanolic sodium ethoxide (each was refluxed for 3 hr), he concluded that basic strength was immaterial (however, it may be relevant that boiling pyridine, although a weaker base, was 35°C hotter). Dimroth also showed that retrogression, which was best achieved by refluxing in a neutral solvent, became rapid only above a critical temperature (e.g., in ethanol, it required 150°C). In every example, retrogression was (at equilibrium) far from complete. For example, 4-amino-5-ethoxycarbonyl-3-phenyltriazole came to equilibrium when only 23% of the primary amine had been reformed. Complete dissolution was found to be essential for obtaining equilibrium. The dielectric constant of the solvent exerted no effect. The rate of the reaction **49** \rightarrow **50** increased with time, because the product provided acidic catalysis. The acidic nature of the product facilitated its separation, by cold alkali, from unchanged starting material (09LA183; 10LA127).

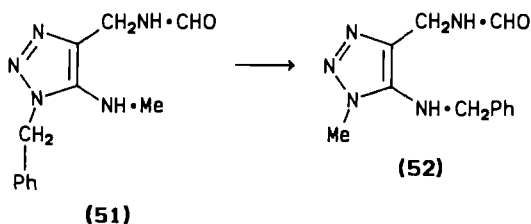
Other Dimroth rearrangements, where the 3-phenyl group carried a variety of substituents, were reported in Refs. 60CB2001 and 80FES298, and the kinetics of such reactions were recorded by Lieber (57JOC654; 57JA5962). Some useful ^1H -NMR characteristics of the two kinds of isomer were discussed in Section II,D. The extraordinary case, in which 4-amino-3-phenyltriazole-5-carboxamide rearranged upon monoacetylation but underwent retrogression when diacetylated, was described in Section III,A,1.

The Dimroth rearrangement has been observed for many other rings including six-membered rings. Reviewing this large field, D. J. Brown concluded that two properties of R drive the equilibrium **49** \rightleftharpoons **50** to the right: (a) electrophilicity of this substituent, and (b) even the slightest bulkiness, which disfavors retrogression (68MI1). To test these indications in the triazole series, 4-amino-3-methyltriazole-5-carboxamide was heated alone, or in solvents, at 240°C, and also in 3 *N* ethanolic ammonia at 180°C (4 hr). The starting material was recovered unchanged in every case. Pursuing this line of thought, 4-methylaminotriazole-5-carboxamide was refluxed in cyclohexanol and yielded 4-amino-3-methyltriazole-5-carboxamide (160°C, 1 hr, 97%) [69JCS(C)152]. The same result was obtainable in boiling 1-pentanol (138°C) [81JCS(P1)2344], whereas boiling ethanol did not suffice. These results enable 3-methyltriazoles to be made without using the easily detonating reagent methyl azide.

The influence of a 3-benzyl group was found to be intermediate between those exerted by the 3-phenyl and 3-methyl groups. Thus 4-amino-3-

benzyltriazole, refluxed in butanol until equilibrium was achieved (118°C, 3 hr), gave a 49:50 ratio of 3:1. In reverse, 4-benzylaminotriazole, boiled with butanol (3 hr), came to equilibrium at the same ratio. However, when 4-amino-3-benzyltriazole was refluxed with cyclohexylamine (pK_a 10.6) (134°C, 3 hr), the equilibrium ratio became 1:3 [70JCS(C)230]. The rearrangement and retrogression of the 5-carboxylic acid and 5-carboxamide of the above compounds are described in the same report.

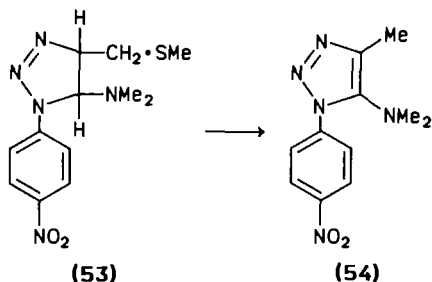
In conclusion, following are some examples where a methyl and a benzyl group exchange places. 3-Benzyl-5-formamidomethyl-4-methylaminotriazole (51), refluxed in octanol, gave 4-benzylamino-5-formamidomethyl-3-methyltriazole (52) (195°C, 6 hr, 67%). Similarly, 3-benzyl-4-methylaminotriazole-5-carboxamide, heated with formamide, produced some 4-benzylamino-3-methyltriazole-5-carboxamide (190°C, 1 hr, 25%) [81JCS(P)2344]. A similar exchange, which occurred during the formylation of 5-aminomethyl-3-benzyl-4-methylaminotriazole at room temperature, was described in Section III,A,1.



E. AROMATIZATION: THE OXIDATION OF TRIAZOLINES TO TRIAZOLES

The many available syntheses of 4-amino-4,5-dihydrotriazoles, also called 4-amino- Δ^2 -triazolines, (see Section V) raises the question of their usefulness as intermediates for making 4-aminotriazoles. In fact, many triazolines have been aromatized, and in good yields, by simple treatment with potassium permanganate (66CB475; 72JHC717; 78S694). Unfortunately, this oxidation has not always worked well with 4-aminotriazolines, which, when subjected to dilute acid or alkali, or even gently heated, tend to lose the elements of ammonia [78BSF(2)485]. This deamination can be lessened by a substituent in the 5 position, but other difficulties may then emerge. For example, 3-*p*-cyanophenyl-4-dimethylamino-5-methyltriazoline, gently treated with potassium permanganate, gave 3-*p*-cyanophenyl-5-methyl-4,*N*-methylformamidotriazoline (78S743).

Nevertheless, several successes are recorded. For example, 4-diethylamino-5-diethylaminomethyl-3-*p*-nitrophenyltriazoline was aerobically oxidized to



the related triazole when boiled with ethanolic sodium hydroxide (1 hr, 60%). The same report presented six related examples [72JCS(P1)769]. Again, 4-dimethylamino-3-*p*-nitrophenyl-5-methylthiomethyltriazoline (**53**) was converted to 4-dimethylamino-3-*p*-nitrophenyl-5-methyltriazole (**54**) (with loss of MeSH) when refluxed with *tert*-butanolic potassium *tert*-butoxide (10 hr, 60%). Several similar examples were presented [77JCS(P1)2365]. For another method, see Section IV,B.

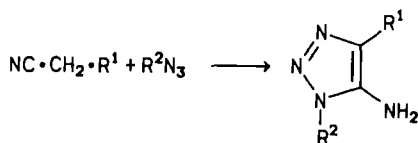
IV. Synthesis of 4-Aminotriazoles

For preparing a required 4-aminotriazole, several good approaches are available. Of the syntheses that begin with noncyclic material, that discussed in Section IV,A has the greatest convenience and versatility, but the resulting 4-amino group is inevitably primary. Tertiary amines are provided by methods discussed in Sections IV,B and C. Alternatively, it is often convenient to transform a heterocycle that belongs to a different system, as discussed in Section IV,E. Finally, a synthesis can be used that introduces into the 4-position a substituent that can be modified to an amino group (Section IV,F).

A. FROM AZIDES AND CYANOMETHYLENE COMPOUNDS

Synthesis from azides and cyanomethylene compounds, discovered by Dimroth [02CB4041], was developed for a range of substituted phenyl azides by Lieber *et al.* (57JOC654) and by Dornow and Helberg (60CB2001) and also for benzyl azide by Hoover and Day (56JA5832). Essentially, it is a base-assisted 1:3-dipolar cycloaddition, taking place across a pair of carbon atoms, one of which must be present as CN and the other as an activated CH₂ group. The reaction is exemplified by Scheme 1.

The reaction, which is not concerted, begins with an attack by the cyanomethylene anion (RCH⁻—CN) on the electrophilic terminal nitrogen



Scheme 1

atom of the azide. This gives an open-chain triazene (several of these have been detected). Finally, the carbon atom of the cyano group is attacked by the azide nitrogen atom nearest to R^2 in Scheme 1 (57JOC654; 71MI1; 72JA2530). Because addition has never been found to occur in the reverse sense, the products have been used to establish any uncertain orientation arising from other azide-based triazole syntheses.

In the starting nitrile, R^1 is most often Ph, CONH_2 , CO_2Me , or another CN group (see Scheme 1). Aryl and vinyl azides perform readily, benzyl azide less so, and saturated alkyl azides rather sluggishly. Hydrazoic acid and most acyl azides do not react. Benzyl azide is often used when the aim is eventually to have no substituent in the 3 position of the triazole, the protective group being removed as in Section III,A,2,c. Actually, 4-methoxybenzyl azide, although less ready to give the triazole, supplies a protective group that is more easily removed, namely, by trifluoroacetic acid (65°C , 3 hr, 70%) [82JCS(P1)627]. An alternative form of protection can sometimes be derived from tosyl azide (see later, in this section).

The following examples illustrate different aspects of Scheme 1 in operation. *p*-Chlorophenyl azide, malononitrile, and methanolic sodium methoxide, set aside, gave 4-amino-5-cyano-3-*p*-chlorophenyltriazole (1°C , 1 hr, 98%) (60CB2001). Methanolic sodium methoxide was added dropwise to a mixture of *p*-tolyl azide and phenylacetonitrile (benzyl cyanide); next day, the temperature was raised to 25°C , and the preparation set aside for 10 hr, giving 4-amino-5-phenyl-3-*p*-tolyltriazole (92%) (57JOC654).

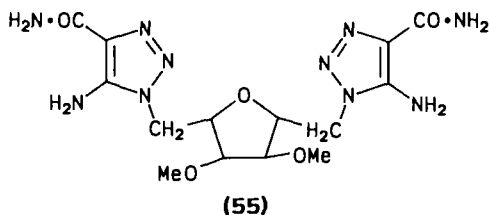
Condensations using benzyl azide required severer conditions: cyanoacetamide and this azide, refluxed with ethanolic sodium ethoxide, produced 4-amino-3-benzyltriazole-5-carboxamide (1 hr, 81%) (56JA5832) [recrystallization from three parts of dimethylformamide gives better purification (85MI2)]. Some reactions that went too slowly in ethanol fared better in an ethereal solvent. When phenylacetonitrile, benzyl azide, and potassium *tert*-butoxide were stirred in tetrahydrofuran, 4-amino-3-benzyl-5-phenyltriazole was obtained in a much improved yield (25°C , 12 hr, 78%). Hexyl azide, treated similarly, gave the 3-hexyl analog (98%) (59JOC134).

The following are examples of use of less common azides. Vinyl azides, including β -styryl azide, gave excellent yields in the *tert*-butoxide method (see above), and β -haloalkyl azides could be used in their place (70JHC361;

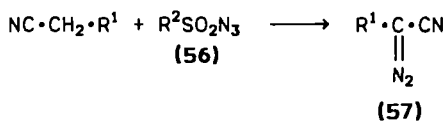
70NKK746). Methyl azidomethyl sulfide and phenylacetonitrile, refluxed in ethanolic sodium ethoxide, produced 4-amino-3-(methylthio)methyl-5-phenyltriazole (8 hr, 15%) (69JHC921).

The azides of carbohydrates furnish analogs of AICAR, a key intermediate in purine biosynthesis (Section VI,B). Thus 2,3,5-tri-*O*-benzyl- α -D-arabinofuranosyl azide, stirred with cyanoacetamide and potassium hydroxide in aqueous dimethylformamide, yielded 4-amino-3-(2,3,5-tri-*O*-benzyl- α -D-arabinofuranosyl)triazole-5-carboxamide (0–25°C, 3 hr, 72%) (72JMC883). The β anomer of this azide gave the α anomer of the triazole because of a transformation, later found avoidable (74USP3826803). Again, 2,3-*O*-isopropylidene-5-*O*-trityl- β -D-ribofuranosyl azide and cyanoacetamide similarly gave 4-amino-3-(2,3-*O*-isopropylidene-5-*O*-trityl- β -D-ribofuranosyl)triazole-5-carboxamide (70%). The mannopyranosyl analog was made similarly. A butyldiphenylsilyl group could usefully replace the trityl group (82T103).

A double-headed example, 2,5-anhydro-1,6-bis(4-amino-5-aminocarbonyltriazol-3-yl)-1,6-dideoxy-3,4-di-*O*-methyl-D-glucitol (**55**), was similarly prepared from 1,6-diazido-1,6-dideoxy-3,4-di-*O*-methyl-2,5-anhydro-D-glucitol (25°C, 15 hr, 49%). [Note: glucitol (sorbitol) is a hexitol] (83ACH443).



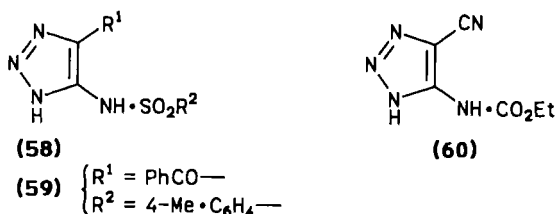
Sulfonazides (**56**) do not, under the conditions described above, react according to Scheme 1 with nitriles. Instead, the azide chain breaks, and diazonitriles (**57**) are formed as in Scheme 2 (75LA2159). This course can be circumvented by carrying out the reaction in water, and at a concentration of alkali in excess of 2 *N*. The reaction then proceeds as in Scheme 1 but with instantaneous rearrangement to give **58**. Thus benzoylacetonitrile and tosyl azide, vigorously agitated in 6 *N* sodium hydroxide, produced *N*-(5-benzoyltriazol-4-yl)-*p*-toluenesulfonamide (**59**) (25°C, 5 min, 30%) (78LA1241).



Scheme 2

Originally, it was found impossible to remove a protective tosyl substituent from the 4-amino group of a triazole. For example, neither hydrogen chloride in dioxane (25°C, 24 hr, 75%) nor 1.2 *N* ethanolic sodium hydroxide (80°C, 14 hr, 71%) affected the tosyl group of 4-tosylamido-5-cyanotriazole while converting the CN to CO₂NH₂ in the stated yields (75LA2159). Later, it was found that **59** could be detosylated to 4-amino-5-benzoyltriazole by stirring with concentrated sulfuric acid (25°C, 20 min, 59%) (78LA1241). If this reaction should turn out to be general, tosyl azide would offer an attractive alternative to benzyl azide for initiating syntheses where the goal is a 4-aminotriazole unoccupied in the 3 position.

Some related azides have been investigated also. Methanesulfonyl azide and malononitrile, stirred vigorously with 2.5 *N* sodium hydroxide and ether, gave 5-cyano-4-methylsulfonamidotriazole (5°C, 1 hr, 92%). Dimethylcarbamoyl azide (Me₂NCON₃) and malononitrile similarly gave 5-cyano-4-dimethylureidotriazole (63%). In neither example was the protective group removed. However, the same authors found that ethyl azidoformate [EtO C(=O)N₃] directly produced 4-amino-5-cyanotriazole (58%), for which **60** was the presumed intermediate (73BSF3442).



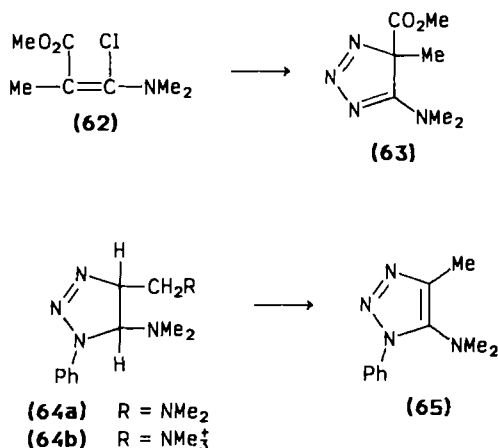
Turning to less common nitriles used in Scheme 1, we find that cyano-*N*-methylacetamide (NCCH₂CONHMe) and 4-azidophenylacetic acid, stirred in ethanolic sodium ethoxide, gave *p*-(5-*N*-methylcarboxamido)-4-aminotriazol-3-ylphenylacetic acid (25°C, 5 hr, 90%) (80FES298). Similarly, cyano-*N,N*-dimethylacetamide and phenyl azide gave 4-amino-3-phenyltriazole-5-*N,N*-dimethylcarboxamide (1°C, 1 day, 74%) [71 JCS(C)706]. Diethyl cyanomethanephosphonate [NCCH₂P(=O)(OEt)₂] and phenyl azide similarly treated gave diethyl 4-amino-3-phenyltriazol-5-yl]-phosphate (10°C, 3 hr, 76%); four related examples are given in the same report (73LA578).

This section will conclude with examples of the use of malonamideamidine [H₂NCOCH₂C(=NH)NH₂] (which may be regarded as cyanoacetamide plus the elements of ammonia) in Scheme 1. Thus this amidine and phenyl azide, refluxed in sodium ethoxide, yielded 4-amino-3-phenyltriazole-5-carboxamide (1 hr, 33%); benzyl azide reacted similarly (38%) (57YZ455). The following example is both unusual and of preparative value. Malon-

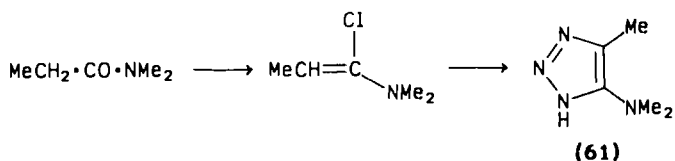
amideamidine (49JBC89; 51JA2763) and tosyl azide stirred in 3 *N* methanolic sodium methoxide, deposited 4-aminotriazole-5-carboxamide (0–20°C, 15 hr, 86%); and methanesulfonyl azide gave 84% of the same product [70CI(L)92].

B. FROM AZIDES AND CHLOROENAMINES

Synthesis from azides and chloroenamines, a little explored method, has some advantages over Method A: it can make use of sodium azide and it can introduce a tertiary amino group in the 4 position. A simple example is shown as Scheme 3. The tertiary amide, with hydrogen chloride and phosgene in dichloromethane, gave the α -chloroenamine (20°C, 5 days, 45%), which, when stirred with sodium azide in acetonitrile, produced 4-dimethylamino-5-methyltriazole (**61**) (–20°C, 60%); the preparation of 5 analogs was also described (80TL223). When phosgene and the amide were condensed under basic conditions, and the product refluxed with methanolic sodium methoxide, a different enamine (**62**) was formed (80%). This, stirred with sodium



azide in acetonitrile, gave one of the rarely encountered 4*H*-triazoles (**63**) whose structure was confirmed by X-ray crystallography. When refluxed with methanolic potassium hydroxide, **63** was converted to **61** (85%) (80CC940).



Scheme 3

In a more complex version of this reaction, propenal was combined with two equivalents of dimethylamine to give $\text{Me}_2\text{NCH}_2\text{CH}=\text{CHNMe}_2$, which, when stirred with phenyl azide in chloroform, furnished 4-amino-5-dimethylaminomethyl-3-phenyl-4,5-dihydrotriazole (**64a**) (25°C, 2 hr, 35%). To achieve aromaticity without loss of C-5, the leaving power of the aliphatic amino group was boosted by quaternizing it as in **64b** with methyl iodide in acetonitrile (25°C, 30 min, 60%). This amine, refluxed with *tert*-butanolic potassium *tert*-butoxide, yielded 4-dimethylamino-5-methyl-3-phenyltriazole (**65**) (80°C, 60%) [80JCS(P)141].

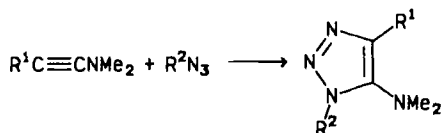
C. FROM AZIDES AND YNAMINES

Synthesis from azides and ynamines, illustrated in Scheme 4, has the advantages claimed for method B; also, there is greater experience in applying it. The preparation of ynamines, which are stable substances, has been reviewed [67AG(E)767]. Some examples of their use follow.

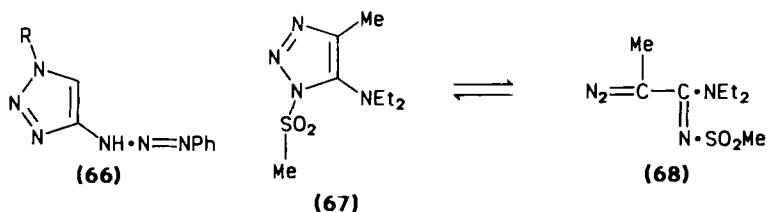
1-Dimethylamino-2-phenylacetylene and phenyl azide gave 4-dimethylamino-3,5-diphenyltriazole (59% yield, conditions not specified) [66AG(E)585]. *N,N*-Diethyl-*N*-2-(ethylthio)ethynylamine and 4-nitrophenyl azide, stirred in ether (light and air excluded), produced 4-diethylamino-5-ethylthio-3-*p*-nitrophenyltriazole (25°C, 4 hr, 56%); several analogs were also described, also NMR and MS data (78CB183).

1-Diethylaminopent-3-en-1-yne, refluxed with phenyl azide in benzene, furnished 4-diethylamino-3-phenyl-5-propenyltriazole (3 hr, 52%); *p*-nitrophenyl azide gave a 75% yield of the corresponding product (84ZOR449). Acetylenemagnesium bromide ($\text{HC}\equiv\text{CMgBr}$) and phenyl azide, stirred in tetrahydrofuran, gave 1-phenyl-4-phenyldiazoaminotriazole (**66**) (25°C, 24 hr, 30%), which, when heated in 10% sulfuric acid until dissolved, yielded 4-amino-1-phenyltriazole (66%) (67ZOR2189). 2-Trimethylsilylethynyldiethylamine ($\text{Me}_3\text{SiC}\equiv\text{CNEt}_2$) reacted with phenyl azide to give 4-diethylamino-3-phenyl-5-trimethylsilyltriazole; also described were many analogs in which ethyl and methyl groups were variously replaced by phenyl and also other types where silicon was replaced by germanium or tin (76CB370).

The use of acyl azides in this reaction is not so straightforward. 1-*N,N*-Diethylaminopropyne ($\text{MeC}\equiv\text{CNEt}_2$) reacted conventionally with ethyl



Scheme 4

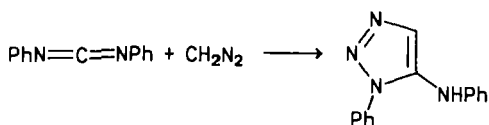


azidoformate ($\text{N}_3\text{CO}_2\text{Et}$) in carbon tetrachloride (25°C) to give 4-diethylamino-3-ethoxycarbonyl-5-methyltriazole. Attempted purification, however, partly isomerizes the product to the 2-ethoxycarbonyl isomer plus a little of the 1-ethoxycarbonyl analog (all recognized by ^1H NMR). Base catalysis by the aminopropyne had caused the rearrangements. Ethoxyacetylene behaved similarly with ethyl azidoformate [72CI(L)886]. 1-Dimethylamino-2-phenylacetylene and benzoyl azide formed what was reported as 3-benzoyl-4-dimethylamino-5-phenyltriazole (71% yield, conditions not given) [66AG(E)585]; however, later investigators claimed that it was really the 2-benzoyl isomer [72CI(L)886].

The following examples report the published orientation, but the reader will keep in mind the possibility of isomerization. Methyl dimethylaminopropiolate ($\text{Me}_2\text{NC}\equiv\text{CCO}_2\text{Me}$) and ethyl azidoformate, stirred in tetrahydrofuran, gave 4-dimethylamino-3-ethoxycarbonyl-5-methoxycarbonyltriazole (25°C , 3 hr, 70%). 1-Dimethylaminobut-1-yn-3-one similarly gave 5-acetyl-4-dimethylamino-3-ethoxycarbonyltriazole (80%) (69HCA2641).

Diphenylphosphinyl azide [$\text{Ph}_2\text{P}(=\text{O})\text{N}_3$] and 1-diethylaminoprop-1-yne, refluxed in benzene, yielded 4-diethylamino-5-methyl-3-diphenylphosphinyltriazole (3 hr, 49%), while diethylphosphorazidate [$(\text{EtO})_2\text{P}(=\text{O})\text{N}_3$] gave the unstable 3-diethoxyphosphinyl analog (70JOC2027). *N*-[(Diphenylthiophosphoro)ethynyl]diphenylamine, stirred with *p*-tosyl azide in chloroform, produced 4-diphenylamino-5-diphenylthiophosphoryl-3-*p*-tosyltriazole (25°C , 30 days, 31%); many analogous products are described in the same report [74CB2513].

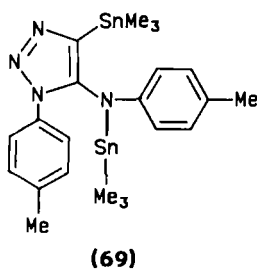
Because of the tertiary nature of the 4-amino group produced by this reaction, no question of a Dimroth rearrangement arises. However, another form (ring-chain) of isomerism is often encountered, kept in check only by favorable electronic disposition. Thus methylsulfonyl azide and 1-*N,N*-diethylaminoprop-1-yne gave 4-diethylamino-5-methyl-3-methylsulfonyltriazole (67) which is in equilibrium with *N,N*-diethyl-*N'*-methylsulfonyl-2-diazopropionamidine (68) (73LA1505). This phenomenon (see Section III,D,1) has been intensely studied with respect to the effect of substituents on the equilibrium, which, in the above example, favors mainly the triazole (70JOC3444; 70JPS1694; 70TL2823; 72CB2963).



Scheme 5

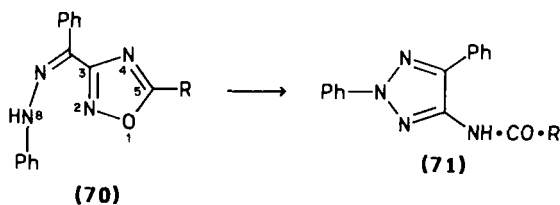
D. FROM DIAZOMETHANE AND CARBODIIMIDES

Synthesis from diazomethane and carbodiimides, of rather limited scope, can be traced to Rotter's observation that diazomethane and diphenylcarbodiimide, mixed in ether, gave 4-anilino-3-phenyltriazole (Scheme 5) (25°C, 4 days, 41%) (26M353; 75CCC1199). Refluxing *p*-tolylcarbodiimide and diazomethane in ether precipitated 3-*p*-tolyl-4-*p*-toluidinotriazole (2 hr, 33%), obtainable in 80% yield by the action of acid on **69**. The latter was prepared by refluxing bis(trimethylstannyl)diazomethane and di-*p*-tolylcarbodiimide in ether (2 hr, 96%) [71JCS(C)3910].



E. FROM OTHER HETEROCYCLES

1,2,3-Triazoles can be made, in good yields, from 1,2,4-oxadiazoles and from 8-azapurines. Both the (*Z*)- and the (*E*)-phenylhydrazones of 3-benzoyl-5-*R*-1,2,4-oxadiazoles (where *R* is H, Me, or Ph) (**70**) undergo general base catalysis to give the isomeric 4-acylamino-2,5-diphenyltriazoles (**71**). The reactions were followed kinetically, at 40°C, while catalyzed severally by sodium methoxide, sodium phenoxide, or piperidine in methanol, aqueous dioxane, and benzene, respectively. In this internal nucleophilic reaction, the formation of the N-8—N-2 bond, and the rupture of the N-2—O bond were found to be concerted. The rate of rupture of the N-2—O bond, in the transition state, depended on the nucleophilic character of N-8, as determined by substituents inserted into the aryl ring attached to N-8 [81AHC(29)141; 82JCS(P1)165; 84JCS(P1)785; 84JCS(P2)541].



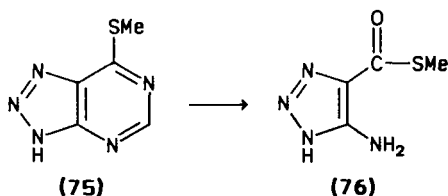
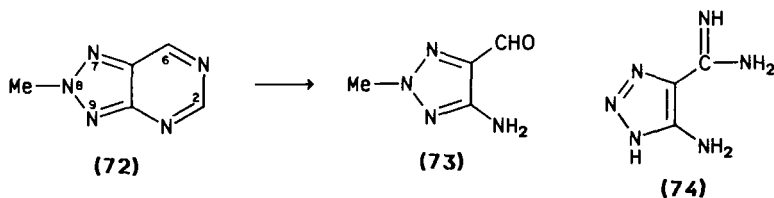
8-Azapurines undergo ring fission to give many kinds of 1,2,3-triazoles, often in excellent yields. At first sight, it may not seem rewarding to prepare triazoles in this way, particularly when the azapurine itself has to be made from a triazole. However, in practice, this approach has often furnished triazoles with patterns of substitution that would be laborious, or even impossible, to prepare by any other known method.

Section III,C of a recent review on 8-azapurines records many examples of these degradations [86AHC(39)117]. It will suffice here to draw attention to examples of preparative importance.

(1) *N*-Alkyl- or aralkyl-8-azapurines (e.g., **72**), in *N*-hydrochloric acid, gave the corresponding 4-amino-5-formyltriazoles (e.g., **73** from **72**) (25°C, 1 day, 96%). When a 6-alkyl group was also present in the azapurine, the corresponding 5-ketone was formed [77JCS(P1)1819; 79CPB2431].

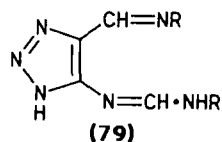
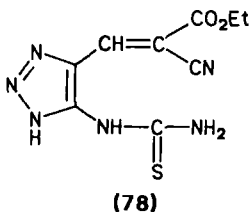
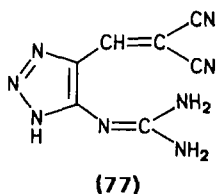
(2) 6-Amino-8-azapurine, and its 7-, 8-, and 9-methyl (also 9-benzyl) derivatives, were converted to amidines of type **74** in boiling *N* hydrochloric acid (1–4 hr, 75–98% yields) [74JCS(P1)2030].

(3) 6-Methylthio-8-azapurine (**75**) gave 4-amino-5-(methylthio)-carbon-yltriazole (**76**) when refluxed with *N* hydrochloric acid (15 min, 90%), and the 7-, 8-, and 9-methyl (also 9-benzyl) derivatives behaved similarly [69JCS(C)2379].



(4) Michael reagents such as malononitrile and ethyl cyanoacetate reacted with 8-azapurine and its 2-amino, 2-oxo, and 2-thioxo derivatives to give complex triazoles such as **77** and **78** in excellent yields [73JCS(P1)1620].

(5) 8-Azapurine and its 2-substituted derivatives reacted, often quantitatively, with aldehyde-trapping reagents, such as 1,1-dimethylhydrazine, hydroxylamine, and methoxyamine, to give triazoles such as **79** [73JCS(P1)1625].



F. FROM OTHER TRIAZOLES, BY METATHESIS

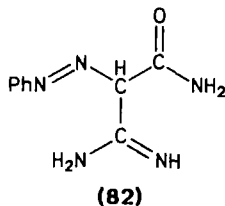
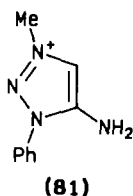
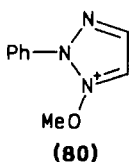
Several synthetic methods are available for inserting, in the 4 position of a triazole, a group that is readily convertible to an amino group. Thus 1-morpholino-2-nitroethylene (from morpholine, nitromethane, and ethyl ethoxymethylenemalonate) was refluxed in ethanol with tosyl azide to give 4-nitrotriazole (12–48 hr, 60%) (66TL6043; 68G949; 71JHC51). 4-Nitrotriazole was also prepared by cleavage of 3-(2,4-dinitrophenyl)-4-nitrotriazole with methanolic sodium methoxide (70OPP117). 1-Morpholino-2-nitroethylene and phenyl azide, when heated in a sealed tube, produced 4-nitro-1-phenyltriazole (100°C, 10 hr, 60%) (68G949). This triazole has also been made by refluxing 1-bromo-1-nitro-2-phenylethylene in ethanol with sodium azide (3 hr, 60%). This and the preparation of several analogs is described in Refs. 75URP469702, 75ZOR2506, and 79ZOR1168. 1-Nitro-2-phenylethylene, heated with phenyl azide in toluene (130°C, 17 hr, 37%) gave 1,5-diphenyl-4-nitrotriazole (67CC918) and not the corresponding triazoline as published originally (66JPR199).

In the final step, 4-nitrotriazole was hydrogenated, in ethanol over palladium, to give 4-aminotriazole (60 psi, 25°C, 6 hr, 92%) (70JHC1159), whereas 5-methyl-4-nitro-1-phenyltriazole was hydrogenated to the amine over palladium in ethyl acetate at atmospheric pressure (25°C, 90%) (68G949). 1,5-Diphenyl-4-nitrotriazole, heated with platinum oxide in hydrazine hydrate, furnished 4-amino-1,5-diphenyltriazole (93%) (66JPR199); 4-nitro-2-β-D-ribofuranosyltriazole, treated with palladium and hydrazine hydrate in methanol, gave the corresponding amine (25°C, 93%) (72JHC1195).

Several Curtius reactions have been employed to produce a primary amino group. Triazole-4-carboxylic acid [from acetylene-1-carboxylic acid and hydrazoic acid in chloroform (46% yield)] was esterified (70%), then converted to the hydrazide (71%) and on to the urethane (52%) and 4-aminotriazole (20%) (57YZ452). The final stage went better for 4-amino-5-methyltriazole, which achieved a 53% throughput from the urethane (76JHC589). 4-Amino-1-methyltriazole was obtained in 64% yield from 4-ethoxycarbonyl-1-methyltriazole in this way (59ACS888).

Possibilities for replacing a chlorine atom by an amino group are variable. 4-Chloro-3-methyltriazole was easily replaced by the anilino group (98°C, 6 hr), whereas 4-chloro-1-methyltriazole was not attacked under these conditions (55LA207). 4-Bromo-3-methyltriazole and ethanolic ammonia gave 4-amino-3-methyltriazole (100°C, 10 hr, 22%) (59ACS888), whereas no reaction occurred with piperidine at 200°C (85MI2).

5-Hydroxytriazole coupled with diazotized aromatic amines in the 4-position to give phenylazotriazoles, which could be reduced to primary amines (58ACS1236). 3-Methoxy-2-phenyl-1,2,3-triazolium tetrafluoroborate (**80**) (made from 2-phenyltriazole 3-oxide and trimethyloxonium tetrafluoroborate) was converted by ammonia in acetonitrile to 4-amino-2-phenyltriazole (20°C, 3 days, 79%) [81JCS(P1)503].



G. MISCELLANEOUS SYNTHESSES

It remains to describe some little used syntheses that may have more general application.

1-*p*-Nitrophenyl-3-(cyanomethyl)triazene ($\text{O}_2\text{NN}=\text{NHCH}_2\text{CN}$), stirred with basic alumina in chloroform, gave 4-amino-3-*p*-nitrophenyltriazole (25°C, 7 days, 80%). Several other substituted phenyl derivatives are presented in this report. When this triazene was refluxed with ethanol, 4-*p*-nitroanilino-triazole resulted, by rearrangement (2 hr, 99%) (81JOC856). Similarly, 1-phenyl-3-(cyanomethyl)-3-methyltriazene, stirred with hydrogen chloride in ether, produced 4-amino-1-methyl-3-phenyltriazolium chloride (**81**) (25°C, 20 min) (70JOC3451).

The hydrazone made from chloral and *p*-tolylsulfonhydrazide ($\text{MeC}_6\text{H}_4\text{SO}_2\text{NHN}=\text{CHCCl}_3$) and an excess of benzylamine furnished 4-benzylamino-3-benzyltriazole (25°C , 1 hr, 30%) [84EUP(A)103840].

Phenylmalonamideamidine (82), heated with ammoniacal cupric sulfate, gave 4-amino-2-phenyltriazole-5-carboxamide (100°C , 3 hr, 95%) (56JA5848).

Sulfonylimidodiazooacetates [$\text{RSO}_2\text{N}=\text{C}(\text{OEt})\text{CH}=\text{N}_2$], where R may be alkyl or aryl, in ethanolic ammonia, produced various 4-alkyl- or 4-arylsulfonamidotriazoles (0°C , 2 days, 80–90%). Primary aliphatic amines in tetrahydrofuran gave the 3-alkyl derivatives of these triazoles (0°C , 2 days, 85–95%), but aromatic amines did not react (76G1).

Finally, should we reconsider this old, neglected example? Oxalic acid amidoxime phenylamidrazone [$\text{H}_2\text{N}(\text{HON}=\text{C})\text{CC}(=\text{NH})\text{NHNHPh}$], heated with water at 150°C , yielded 4,5-diamino-2-phenyltriazole [(1897LA(295)129)].

H. SOME HELP IN CHOOSING THE BEST ROUTE

Most syntheses of 1,2,3-triazoles start with an organic azide. Houben–Weyl's "Methods of Organic Chemistry" provides 60 pages on the preparation, reactions, and hazards of these substances [65HOU(10/3)777]. All azides should be handled with respect to their potential toxicity and explosiveness. The aryl and aralkyl azides have a good safety record. The preparations of many aryl azides are cited in this reference (57JOC654). At the other end of the safety scale, methyl azide has caused devastating explosions even when every recommended precaution has been taken [65HOU(10/3)781, 802]. Its use, for preparing 3-methyltriazoles, can be avoided by using a simple Dimroth retrogression to transfer a methyl group from 4-NHMe to N-3 (see Section III,D,2).

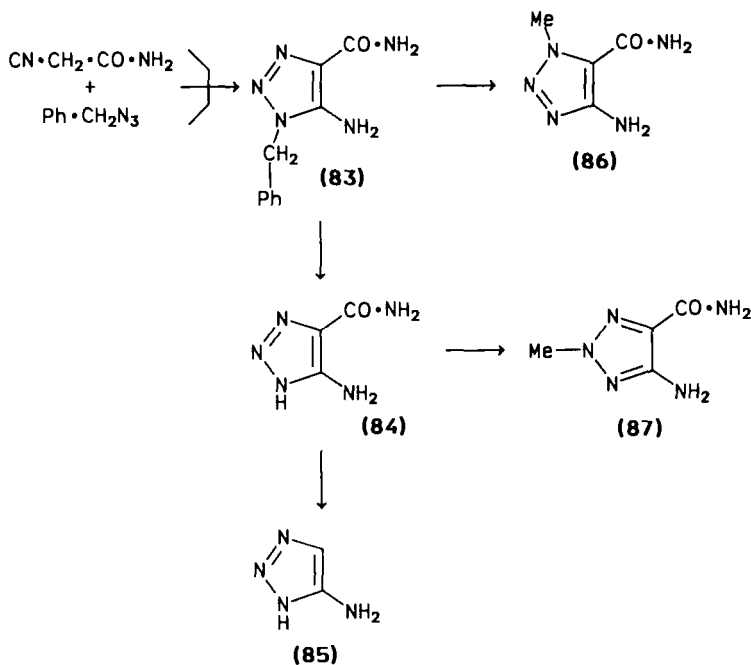
Benzyl azide, often required, is best made as Curtius and Ehrhart originally did (22CB1565) with one modification to avoid troublesome emulsification. When refluxing is completed, the mixture should be cooled to 25°C and added to water (2000 ml for a 40-g benzyl chloride batch), then extracted with chloroform (3×175 ml). The combined extracts are washed with water (200 ml) and dried (CaCl_2). After vacuum distillation, the product should be stored in a refrigerator (85MI2).

Houben–Weyl separately lists preparation of the azides of carboxylic and sulfonic acids [(52HOU(8)680) and (55HOU(9)653), respectively]. Ethyl azidoformate is readily made as in Ref. 65JA1953.

Of all methods for synthesizing 4-aminotriazoles, the most convenient and versatile is the condensation of azides with cyanomethylene compounds (Section IV,A), although only a primary amino group can be furnished in this

way. A worthwhile start, for entering many different areas of the 4-aminotriazole field, is provided by Hoover and Day's preparation of 4-amino-3-benzyltriazole-5-carboxamide, as Scheme 6 shows. This triazole (**83**) is readily debenzylated to **84** (Section III,A,2,c) which, by methylation (Section III,A,2,b), after protective formylation (Section III,A,1), gives **87** (a process equally successful for 2-benylation). Again, **83**, after a quaternizing methylation followed by debenzylation (Section III,A,2,c), produces **86**. All these reactions, which lead from the 3- to the 1- and 2-substituted series, are straightforward and give excellent yields.

The CONH_2 group, wherever it is shown in Scheme 6, can be modified to CO_2H , or CN , or replaced by hydrogen (e.g., **84** \rightarrow **85**) (Section III,C,3). 4-Amino-3-benzyl-5-ethoxycarbonyltriazole may be made by condensing ethyl cyanoacetate with benzyl azide (56JA5832), and its ester function transformed to the alcohol or aldehyde (Section III,C,1). Aldehydes can also be made from the 5-nitriles (Section III,C,4). An aminomethyl group is obtained in the 5 position by reducing a 5-nitrile (Section III,C,4). The 5-amidino and the 5-(methylthio)carbonyl groups are best obtained by degradation of an 8-azapurine (Section IV,E).



Scheme 6

Alternative syntheses for 4-aminotriazoles without substituents on nuclear nitrogen atoms are described in Section IV,A, namely, the action of ethyl azidoformate or tosyl azide on activated cyanomethylene compounds, or tosyl azide on malonamideamidine; however, the generality of these reactions is yet to be demonstrated. Another approach is available through the reduction of 4-nitrotriazoles, obtained from 1-morpholino-2-nitroethylene (Section IV,F).

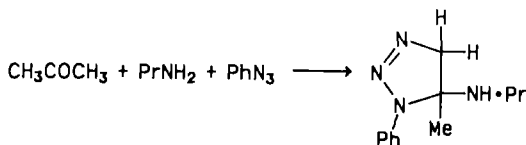
Phenyl groups may be placed in the 3 position by the cyanomethylene synthesis (Section IV,A), in the 2 position by Taylor's synthesis (Section IV,G), or in the 1 position by the use of either acetylenemagnesium bromide (Section IV,C) or 1-morpholino-2-nitroethylene (Section IV,F) with phenyl azide.

Tertiary 4-amino groups are best engineered by the acetylenic approach (Section IV,C), but there is no direct pathway to secondary amines. A methyl group is easily inserted in a 4-NH₂ group by methylation, provided that a ring nitrogen atom is already alkylated (Section III,A,2,b); the introduction of less reactive alkyl groups is an unsolved problem. Fortunately, a benzyl or a phenyl group is readily transferred from N-3 by a Dimroth rearrangement (Section III,D,2).

V. Syntheses of 4-Aminotriazolines

In what follows, the simple word "triazoline" will be used for 4,5-dihydro-1,2,3-triazole. An excellent review of the syntheses and reactions of triazolines enables limiting this section to a discussion of only the bare essentials [85AHC(37)217].

Most syntheses of triazolines begin by combining an amine with an aldehyde or ketone to give an enamine, which is then converted to a triazoline by an organic azide, as in Scheme 7. Alternatively, the three types of starting materials may be present at the start of the synthesis. A primary amino group has been achieved in the 4 position by adding liquid ammonia to a mixture of *p*-nitrophenyl azide and an aldehyde (or ketone), to give a 4-aminotriazoline, which bore a further substituent in the 4 position only if a ketone had been selected; the 5 position bore no substituent if acetone or acetaldehyde had been chosen, but a methyl group if propionaldehyde had been selected, and so on (25°C, 1–7 days, 25–98%) [74ACS(B)425].



Scheme 7

Triazolines with secondary or tertiary amino groups in the 4 position were similarly made by treating a primary or secondary amine (respectively) with an aldehyde or ketone and *p*-nitrophenyl azide in chloroform (25°C, 1–14 hr, 30–98%) (64JA2213; 69G1131). The products isolated from chloroform were usually mixtures of *cis* and *trans* isomers [as determined by ¹H NMR (See Section II,D)], whereas recrystallization from benzene gave the pure *trans* isomer, which was conformationally stable only if a bulky group, such as phenyl, occupied the 5 position [72JCS(P1)997].

Morpholine has been found to be a useful leaving group in these reactions. 1,1-Di-(*N*-morpholino)ethane and *p*-nitrophenyl azide, refluxed in chloroform, gave 3-*p*-nitrophenyl-4-*N*-morpholinotriazoline (30 min, 80%) (67G109). Moreover, both of the morpholine residues were surrendered by 1,1-di-(*N*-morpholino)ethane when it was heated with diethylamine while *p*-nitrophenyl azide was added, giving 3-*p*-nitrophenyl-4-diethylaminotriazoline (60°C, 24 hr, 80%) (67G109). Diethyl ketals, such as 2,2-diethoxybutane, can be used in place of ketones (67G579).

A wide variety of groups can be programmed into the 5 position. Thus, ethyl β -ethylaminomethacrylate and benzyl azide gave 3-benzyl-4-ethylamino-5-methyl-5-ethoxycarbonyltriazoline. Again, β -*N*-piperidinomethacrylonitrile and phenyl azide furnished 5-cyano-5-methyl-4-*N*-piperidino-3-phenyltriazoline (no solvent, 62°C, 3 days, 54%) (75JHC505); the kinetics of this highly regiospecific reaction were also studied (76BSF2025). 3-(Methylthio)propanal, dimethylamine, and *p*-nitrophenyl azide, in benzene, gave 4-dimethylamino-5-(methylthio)methyl-3-*p*-nitrophenyltriazoline (25°C, 12 hr, 45%) [77JCS(P1)2365].

Unsaturated aldehydes and amines give ene-1,3-diamines which combine with aryl azides in chloroform to yield, e.g., 4-methylamino-5-methylaminomethyl-5-phenyltriazoline from propenal, methylamine, and phenyl azide (25°C, 1–36 hr, 60–90%) [72JCS(P1)619; 72JCS(P1)769].

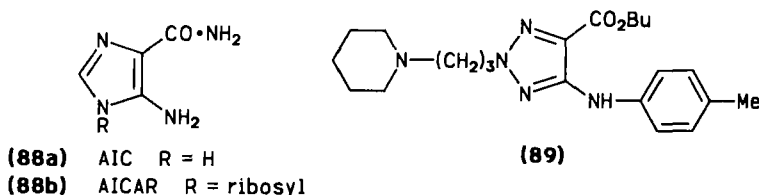
VI. Applications of 4-Aminotriazoles

Various uses have been suggested for 4-amino-1,2,3-triazoles, and many patents have been issued. However, no major commercial products, based on this structure, have yet appeared.

A. BIOLOGICAL AND MEDICAL USES

Although no 1,2,3-triazole has yet been isolated from nature, a 1,2,3-triazolo[4,5-*d*]pyrimidine antibiotic was obtained from *Streptomyces albus*

[86AHC(39)117]. The structural similarity of 4-aminotriazole-5-carboxamide (**84**) to 4-aminoimidazole-5-carboxamide, (**88a**) (known to biochemists as AIC) prompted testing the former as an antagonist of the latter, which, as its riboside (AICAR, **88b**), is an essential step in the biosynthesis of all purines. It was found that **84** prevented the uptake of AIC into the purines of rat and pigeon liver slices (56CPB97). Investigating another facet of the same biosynthesis revealed that the conversion of glycine-¹⁴C (through AICAR) to hypoxanthine, by pigeon liver homogenate, was inhibited more than 50% by 4-acetamidotriazole-5-carboxamide, 4-diazotriazole-5-carboxhydrazide, and 4-diazo-5-cyanotriazole, all substances in which a 4-amino group would be liberated on biodegradation (68MI2).



A set of 4-amino-3-aryltriazoles, each one further substituted by a 5-amide, -ester, or -nitrile group, inhibited these enzymes: adenosine deaminase, guanine deaminase, and xanthine oxidase. Structure-action relationships were discussed (79MII; 85FES73).

The anticancer activity of 8-azaguanine was potentiated by administering the triazole **84** with it to mice in which Ehrlich ascites carcinoma had been implanted. Although **84** had no direct action on the tumor, it reinforced the cytotoxic effect of the azapurine by inhibiting the destructive action of guanine deaminase (69CPB539).

The triazole **84** and some of its derivatives showed antibacterial activity against *E. coli* (68M12), whereas tertiary amines, such as 4-diethylamino-3-p-methoxybenzenesulfonyl-5-methyltriazole, were strongly effective against *B. subtilis* (70JPS1694). 4-*p*-Aminobenzenesulfonamido-2-phenyltriazole is claimed as a bactericide and a conditioner for adding to the food of farm animals (72JAP40050). Bactericidal and fungicidal properties are claimed for 4-amino-2- and -3-ribofuranosyltriazoles and their 5-substituted derivatives (76USP3968103). Improved antibacterial properties are claimed for semisynthetic penicillins that incorporate the 4-aminotriazole moiety (78JAP51091).

4-Aminotriazole-5-carboxylic acid (but not **84**) was found to be incorporated into the RNA of tobacco mosaic virus and of *E. coli*, and it inhibited both organisms, whereas **84** was inert (57BJ323). 4-Anilino-5-ethoxycarbonyltriazoles, in which the benzene ring carries a *m*- or *p*-fluoro or chloro substituent, are claimed as anthelmintics (70GEP2009134). 5-Ethoxy-3-halophenyl-4-morpholino- or 4- β -hydroxyethylamino triazoles are claimed

to be active against the parasitic worms *Schistosoma mansoni*, *Enchytraeus albidus*, and *Tubifex rivulorum* (70GEP2012943).

4-Amino-3-(3,4-dichlorobenzyl)-1,2,3-triazole-5-carboxamide, and related compounds, made by condensing an azide with cyanoacetamide, were strongly coccidiostatic, even at a dilution of 0.001%, in chicken feed (85EUP151528). Several 3-[4-(4-chlorobenzoyl)benzyl] analogs had similar activity (85EUP151529).

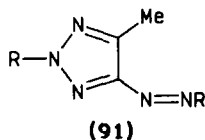
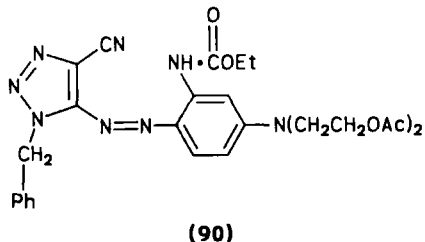
In addition to these chemotherapeutic indications, some pharmacodynamic uses are indicated. 4-Amino-3-*o*-chlorobenzyltriazole-5-carboxamide and related compounds are claimed as useful anticonvulsants (84JAP118775). 5-Butoxycarbonyl-2-(*N*-3-piperidinopropyl)-4-*p*-toluidinotriazole (89) is claimed as a potent vasodilator (83GEP3134842). 1*H*-Triazolo[4,5-*b*]quinol-4-one (99) is claimed to inhibit passive cutaneous anaphylaxis in rats and to be of interest in treating human asthma [80EUP(A)2562].

B. CHEMICAL USES

1. As Dyes and Textile Assistants

4-Amino-2-*p*-methoxyphenyltriazole, when diazotized and coupled with *m*-methoxy-*N,N*-dimethylaniline, is claimed to give a reddish-brown dye suitable for polyester and polyamide fibers (six other examples are cited) (73EGP95438). 4-Amino-2-*p*-anisyl-5-*p*-nitrophenyltriazole, diazotized and coupled with β -naphthol or acetoacetanilide, is claimed to give dispersible dyes suitable for textiles (78EGP131473). 4-Amino-2-*p*-aminophenyl-5-methyltriazole, tetrazotized and coupled to 2-naphthol, is claimed to give a useful azoic pigment (73EGP96708).

4-Amino-3-benzyl-5-cyanotriazole, when diazotized and coupled to 3-ethoxycarbonylamino-*N,N*-di(2-acetoxyethyl)aniline, is claimed to give a dispersible pigment (90) that is used to dye polyester fibers in fast red shades (79GEP2856873). In a development of tartrazine (the traditional pyrazole



yellow dye for wool), the aliphatic compound $\text{MeC(=NOH)C(=NNHR)-N=NR}$ was cyclized by refluxing with dimethylformamide containing sulfuric acid to give **91** ($\text{R} = 2\text{-methoxy-5-sulfophenyl}$). This is claimed to dye woolen and polyamide fibers in wash- and light-fast yellow tones (three other examples cited) (71CZP141765).

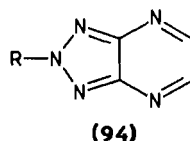
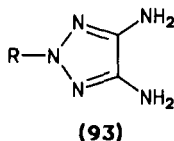
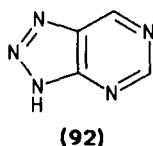
Several triazole derivatives are proposed as UV-controlling agents. 2-(2-Hydroxy-5-chlorophenyl)-4-aminotriazole-5-carboxamide and related compounds are claimed as UV stabilizers for nylon articles, dyed polyester fibers, nitrocellulose lacquer, polyolefins, and as sunscreen agents for the human skin (71GEP2041845). 4-(Triazol-2-yl)-4'-phenylstilbenes are claimed as fluorescent whitening agents for textile fibers (70GEP1917740), as are 4,4'-bis-(5-phenyl-4-acetamidotriazol-2-yl)-2,2'-stilbene disulfonate and related compounds (68FRP1508550).

2. To Prepare More Complex Heterocycles

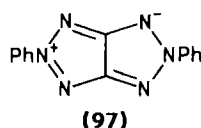
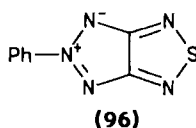
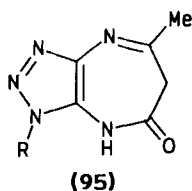
The 4-amino-1,2,3-triazoles are much used, as easily accessible starting materials, for preparing more complex heterocycles. This section will deal first with examples where the 4 and 5 positions of the triazole participate in forming the new ring.

Many standard syntheses of 8-azapurine (**92**) and its derivatives conveniently begin with a 4-aminotriazole that is appropriately carbon substituted in the 5 position. Because these reactions are discussed in a recent review, they will not be listed here [86AHC(39)117].

4,5-Diaminotriazoles, such as **93**, react with 1,2-dicarbonyl reagents to give 1,2,3-triazolo[4,5-*b*]pyrazines, as **94**. Thus 4,5-diamino-2-phenyltriazole and glyoxal, refluxed in ethanol containing acetic acid, gave **94** ($\text{R} = \text{Ph}$) (2 hr, 89%) (78JOC341). Other 1,2-dicarbonyl compounds reacted similarly with this triazole (78JOC341) and with 1-benzyl-4,5-diaminotriazole (72JOC4124). The latter triazole also reacted with ethyl acetoacetate to yield 4*H*,6*H*-1-benzyl-7-methyl-1,2,3-triazolo[5,4-*b*][1,4]diazepin-5-one (**95**) (72JOC4124).

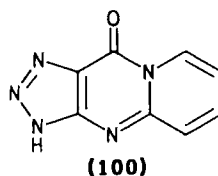
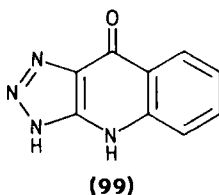
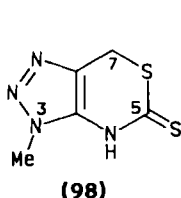


4,5-Diamino-2-phenyltriazole and sulfur monochloride, when refluxed in benzene, produced 5-phenyl-5*H*-[1,2,3]triazolo[4,5-*c*][1,2,5]thiadiazole (**96**) (18 hr, 38%), which belongs to the larger family of heteropentalenes



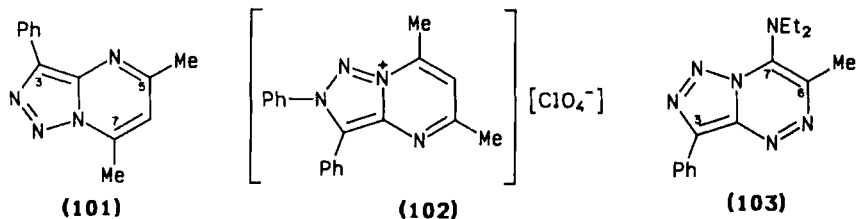
(74BCJ1493). The same triazole was converted to 4-azido-2-phenyl-5-phenylazotriazole, which, when stirred in decahydronaphthalene, furnished 2,5-diphenyl-1,2,3-triazolo[4,5-*d*]1,2,3-triazole (97) (105–160°, 60%); several analogs were also described (70BCJ3587).

A derivative of a hitherto unknown nucleus was produced when 4-amino-5-aminomethyl-3-methyltriazole was refluxed with carbon disulfide and triethylamine in pyridine, which yielded 3-methyl-3,7-dihydro-1,2,3-triazolo[4,5-*d*][1,3]thiazine-5-thione (98) (3 hr, 53%); the 3-benzyl analog was made similarly (63%) [80JCS(P1)2009]. Cyclization of 4-anilino-5-ethoxycarbonyltriazole with polyphosphoric acid produced 1*H*-triazolo[4,5-*b*]quinol-4-one (99) [80EUP(A)2562]. Similarly, ring closure of 4-(2-pyridylamino)triazole-5-carboxylic acid (or its esters) gave 1*H*-pyrido[1,2-*a*]-1,2,3-triazolo[4,5-*d*]pyrimidin-4-one (100) (77GEP2757929). 4-Amino-5-formyl-3-methyltriazole and pentane-2,4-dione, set aside in 20% sulfuric acid, yielded 3,5-dimethyl-3*H*-1,2,3-triazolo[4,5-*b*]pyridin-6-yl methyl ketone (25°C, 8 hr, 75%) (79CPB2861).

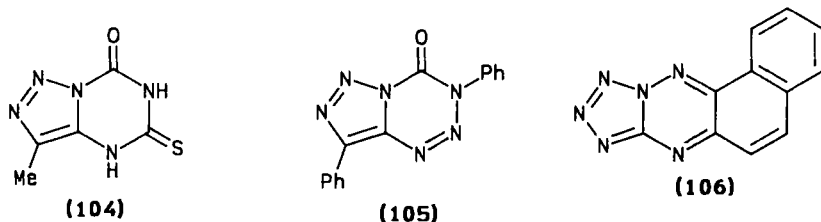


Finally, there are syntheses where the 3 and 4 positions of the triazole become incorporated in a new ring. 4-Amino-5-phenyltriazole, acetylacetone, and sodium hydroxide, when refluxed in ethanol, gave 5,7-dimethyl-3-phenyl-1,2,3-triazolo[3,4-*a*]pyrimidine (101) (10 min, 91%) (three related examples also cited) [71JCS(C)2156]. Similarly, 4-amino-5-phenyltriazole, ethyl acetoacetate, and piperidine, refluxed for 2 hr in ethanol, gave a mixture of 5-methyl-3-phenyl-1,2,3-triazolo[3,4-*a*]pyrimidin-7(4*H*)-one (68%) with the 7-methyl isomer (17%) [73JCS(P1)943]. 4-Amino-5-phenyltriazole, condensed with 1-methylbut-2-en-1-ol in a mixture of trifluoroacetic and perchloric acids, produced 2,3-diphenyl-1,2,3-triazolo[1,5-*a*]pyridinium perchlorate (102) (78KGS1422).

4-Amino-5-phenyltriazole was diazotized and the product stirred with 1-diethylaminoprop-1-yne to yield 7-diethylamino-6-methyl-3-phenyl-1,2,3-triazolo[5,1-*c*][1,2,4]triazine (**103**) (25°C, 15 min, 71%) (two related examples cited) (77S556). Similarly, diazotized 4-amino-5-phenyltriazole, acetylacetone, and sodium acetate, stirred in aqueous ethanol, furnished 6-acetyl-7-methyl-3-phenyl-1,2,3-triazolo[5,1-*c*][1,2,4]triazine (seven analogs also described) (72TL4719).



4-Amino-5-methyltriazole and carbethoxy isothiocyanate, stirred in acetonitrile, gave 3-methyl-5-thioxo-1,2,3-triazolo[1,5-*a*][1,3,5]triazin-7-one (**104**) (25°C, 30 min, 65%) (76JHC589). 5-Phenyltriazole-4-diazonium chloride and phenyl isocyanate, stirred in dichloromethane, provided 3,6-diphenyl-1,2,3-triazolo[5,1-*d*][1,2,3,5]tetrazine-4-one (**105**) (25°C, 41%) (79TL4253). Finally, diazotized 4-aminotriazole was coupled to 2-naphthol. The product, refluxed in methanol, was cyclized to naphtho[2,1-*e*][1,2,3]-triazolo[1,5-*b*] triazine (**106**) (2 days, 80%) (74JHC867).



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58G977

58SA250
59ACS888
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